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Baseline Staging Tests in Primary Breast Cancer Practice Guideline Report # 1-14

Members of the Breast Cancer Disease Site Group

ORIGINAL GUIDELINE: February 8, 2000
MOST RECENT LITERATURE SEARCH: April 30, 2003

Literature searches conducted since completion of the original guideline have found no new evidence relevant to the recommendations made in the guideline report.

SUMMARY

Guideline Questions

- 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?
- 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?
- Is there a role for performing these tests before surgery or, for cases in which they are necessary, should they be performed only after surgery?

Target population

The following recommendations apply to women with newly diagnosed breast cancer who have undergone surgical resection and who have no symptoms, physical signs or biomedical evidence of metastases.

Recommendations

- 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.
- 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.

Methods

Relevant evidence was identified by a systematic search of MEDLINE (1966-April 2003) and the

Cochrane Library (Issue 1, 2003). Reports of case series in which 1) newly-diagnosed breast cancer patients were evaluated by bone scan, liver ultrasound or chest radiograph and 2) the number of cases positive for metastases were reported by stage of disease were eligible for inclusion in the overview of the evidence.

Evidence was selected and reviewed by one member of the Breast Cancer Disease Site Group and one member of the Practice Guidelines Initiative research staff. This practice guideline has been reviewed and approved by the Breast Cancer Disease Site Group, which comprises surgeons, medical oncologists, radiation oncologists, epidemiologists, a pathologist, a medical sociologist and community representatives.

External review of the original practice guideline report by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline was obtained from the Practice Guidelines Coordinating Committee. The Practice Guideline Initiative has a formal standardized process to ensure the currency of each guideline report. This consists of the periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

Key Evidence

- Eleven studies of bone scanning reported between 1972 and 1980 involved a total of 1307 women; bone scans detected skeletal metastases in 6.8% of those with stage I disease, in 8.8% with stage II, and in 24.5% with stage III. A total of 5407 women participated in nine studies of bone scanning reported between 1985 and 1995; in these studies, bone scans detected skeletal metastases in 0.5% of women with stage I disease, in 2.4% with stage II, and in 8.3% with stage III.
- Among 1625 women in four studies of liver ultrasound 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.
- Among 3884 cases in two studies published in 1988 and 1991, chest radiographs detected lung metastases in 0.1% of stage I patients, in 0.2% of stage II, and in 1.7% of stage III.
- False-positive rates ranged from 10 to 22% for bone scanning, 33 to 66% for liver ultrasonography, and 0 to 23% for chest radiography. The false-negative rate for bone scanning was approximately 10%.

Future Research

Future studies should focus on the relationship between nodal status and the rates of detection of metastases by routine baseline testing with bone scan, liver ultrasound and chest radiograph.

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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹ The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

¹ Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

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FULL REPORT

I. 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 these tests before surgery or, for cases in which they are necessary, should they be performed only after surgery?

II. CHOICE OF TOPIC AND RATIONALE

Over 7000 women will develop breast cancer each year in the province of Ontario (1). These patients will all undergo some sort of staging work-up at the time of diagnosis. One of the main purposes of staging is to rule out distant disease that would render the patient incurable with conventional therapy. Staging may occasionally occur before surgery, but is more commonly performed after surgery at the hospital where primary therapy is given. In many cases, these investigations may be repeated at secondary or tertiary referral centres.

Occasionally, false-positive results occur, leading to other expensive tests that negate the results of the original test. These staging tests are expensive (Table 1), time consuming and anxiety provoking. Although it is recognized that women with seemingly localized breast cancer may at some point develop metastatic disease, the clinical experience of the members of the Breast Cancer Disease Site Group (DSG) was that the prevalence of detectable metastases at initial diagnosis is very low in most stages of the disease. Hence, the Breast Cancer DSG decided to carefully review the evidence and indications for routine testing consisting of bone scan, liver ultrasound and chest radiograph in the asymptomatic woman who has undergone surgery for breast cancer.

Table 1. Costs of baseline staging tests, from the Ontario Health Insurance Plan fee schedule (Canadian dollars).

	Technical Fee	Professional Fee
Bone Scan	\$103.80	\$48.10
Ultrasound	\$48.80	\$29.10
Chest Radiograph	\$21.91	\$8.80

Staging in cancer, and more specifically breast cancer, has been a cornerstone in the management of this disease. Some of the reasons cited for baseline testing include: to predict prognosis, to ensure correct treatment, to reassure the patient, to serve as a baseline for follow-up tests, and to help compare results with those from other centres. In the early 1970's and 1980's, surgeons ordered these tests routinely before surgery to decide on whether mastectomy was appropriate. The routine use of these tests persisted over time but they were ordered more in the postoperative period. Though it has become more apparent over the years that the yield of staging tests, whether they are performed before or after surgery, is exceedingly low, the practice has persisted. However, staging tools are in a continuous state of evolution. The tests of today are more sensitive than in the past, thanks both to technical improvements and to the development of newer tests, such as magnetic resonance imaging (MRI) and computerized

tomography (CT). A study in women at high risk for metastases who were being considered for transplant demonstrated that a very aggressive staging program can uncover disease not recognized by standard tests (2). This practice guideline report, however, will limit itself to discussing commonly used techniques in breast cancer staging, i.e., bone scan, abdominal ultrasound and chest radiograph.

In the 1970's, several studies of bone scanning detected quite high rates of metastatic disease in stage I and II cases, ranging from 3.4% to 35.5% (3-6). These studies were based on small numbers of cases, but were quoted frequently and helped to create controversy about staging. Subsequent studies with thousands of patients have rebutted these early data and have shown an exceedingly low rate of true bone scan abnormality. These studies, as well as reports concerning liver ultrasound and chest radiographs, are discussed below.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care, using the methods of the Practice Guidelines Development Cycle (7). Evidence was selected and reviewed by members of the Breast Cancer DSG and methodologists. Members of the Breast DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on baseline staging tests in primary breast cancer, developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guideline Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

The MEDLINE and CANCELIT databases (Ovid) were searched from 1966 to July 1998 using the MeSH headings "breast neoplasms", "neoplasm staging", "neoplasm metastasis", "bone neoplasms/sc", "liver neoplasms/sc" and "lung neoplasms/sc" and the textwords "preop:", "stag:" and "baseline". The search was updated in March and November 1999 and again in April 2000. These terms were also used to search the Cochrane Library (1999, Issues 1 and 4 and 2000, Issue 1). Articles found by the searches, cited in the relevant papers or known to the lead author of this practice guideline were retrieved and reviewed.

Update

The literature search was updated using subject headings (breast neoplasms, neoplasm staging, neoplasm metastases, bone neoplasms/sc, liver neoplasms/sc, lung neoplasms/sc, clinical trial{s}, exp evaluation studies) and text words (breast, mammary, cancer, carcinoma, neoplasm, stage:, baseline). MEDLINE (2000-April 2003), the Cochrane Library (Issue 1, 2003) and the PDQ Clinical Trials Database (http://www.cancer.gov/search/clinical_trials/, accessed

April 30, 2003) were searched for clinical trials of bone scanning, liver ultrasonography or chest radiography as staging tests in breast cancer.

Inclusion Criteria

Studies were eligible for inclusion in this overview of the evidence if they reported the number of women with newly diagnosed breast cancer who had metastases detected by bone scan, liver ultrasound or chest radiograph. These tests could be performed either before or after surgery. Both full reports and abstracts were eligible. Studies were included only if they reported the rates of positive tests by stage of disease and the staging system was similar to that currently in use (see Appendix I).

The primary outcome of interest was the detection rate, that is, the number of patients with abnormal tests that were indicative of metastases divided by the total number of patients tested. Detection rates were calculated by the guideline authors from data appearing in the study reports. Also of interest were the false-positive and the false-negative rates (8); these were given in some of the study reports reviewed for this guideline.

Synthesizing the Evidence

In order to get overall estimates of detection rates, results were pooled across studies. Study results were tabulated according to the stage of disease (I, II and III) and summed across studies. For each stage, the detection rates were pooled by dividing the total number of patients who tested positive for metastases by the total number of patients tested in the studies; the 95% confidence intervals (CI) were calculated for the pooled rates. Results from all stages were also pooled to produce an estimate of the overall detection rate.

IV. RESULTS

Literature Search Results

The literature search described above was not restricted by language; it uncovered three reports on bone scanning published in French and one in German. Because a large body of literature published in English was available and resources for translation were limited, these foreign-language publications were excluded from this practice guideline.

Twenty-two reports published in English of 21 case series evaluating one or more of the staging tests in question met the eligibility criteria above. These are summarized in Table 2.

Table 2. Studies eligible for inclusion in this report.

Staging test evaluated	Number of studies	Reference numbers	Summary of results
Bone scan	20	3, 5, 9-26	Tables 3 & 4
Liver ultrasound	4	21, 24, 27, 28	Table 5
Chest radiograph	2	21, 28	Table 6

Two studies evaluated all three staging tests (21, 22, 28). For one of these studies, Ahmed et al reported the data for bone scan (22) while liver ultrasound and chest radiograph results from the same series of patients appeared in a separate report by Glynne-Jones et al (28). Another study evaluated both bone scan and liver ultrasound (24).

Thirty-three additional studies evaluating bone scanning, four studies of liver ultrasonography and one study of chest radiography were not included in this report because they did not provide data in a format that would allow for analysis by stage of disease.

Update

No additional studies were found by update searches.

Bone Scan

The bone scan is the most commonly used method of detecting bone metastases. Although there is disagreement regarding its accuracy, it is more sensitive than skeletal radiographs (26). The bone scan is a safe procedure (29) that uses injection of the radiopharmaceutical technetium 99 MDP followed by scanning with a gamma camera. Sensitivity rates as high as 98% have been reported, but bone scans can also detect benign processes, and the false-positive rate ranges between 10 and 22% (29). The false-negative rate is estimated at 10% (29). The positive predictive value can be as low as 11.9% depending on how tight the definition of a positive scan is (29). All of these issues apply to staging well women with operable breast cancer. Furthermore, the prevalence of detectable metastatic disease in this population is exceedingly low.

Our literature search identified many studies that addressed the role of bone scans in early breast cancer. In general, studies up to 1980 (Table 3) tended to report higher rates of positive bone scans than those reported after 1980 (Table 4). To reflect this trend, most likely brought about by changes in practice and in bone scan technology, the Breast Cancer DSG felt that it was appropriate to divide the studies into older or more recent and arbitrarily chose 1980 as the cut-off date. Although the study methods used were not always clearly reported, data collection appeared to be retrospective in ten studies (9,12,18-23,25,26) and prospective in ten (3,5,10,11,13-17,24). Bone scans were performed before surgery in eight studies (10-13,15,16,21,25) and after surgery in four (9,14,22,26); the remaining studies included both preoperative and postoperative tests or did not state clearly when the tests were done.

Table 3. Bone scan results by stage of disease, from studies reported up to 1980.

1st author (Reference)	Year of report	# patients with positive bone scan/ #patients in study (%)			
		Stage I	Stage II	Stage III	Total
Hoffman (9)	1972	2/10 (20%)	14/37 (38%)	8/13 (62%)	24/60 (40%)
Citrin (5)	1975	6/49 (12%)	5/26 (19%)	NA	11/75 (15%)
Campbell (3)	1976	15/50 (30%)	9/17 (53%)	8/13 (62%)	32/80 (40%)
Gerber (10)	1977	2/73 (3%)	0/37 (0%)	5/12 (42%)	7/122 (6%)
Baker (11)	1977	1/28 (4%)	0/36 (0%)	10/41 (24%)	11/105 (10%)
Clark (12)	1978	5/71 (7%)	4/99 (4%)	12/31 (39%)	21/201 (10%)
McNeil (13)	1978	0/37 (0%)	2/85 (2%)	6/31 (19%)	8/153 (5%)
Nomura (14)	1978	1/14 (7%)	7/66 (11%)	2/34 (6%)	10/114 (9%)
O'Connell (15)	1978	1/30 (3%)	6/42 (14%)	1/13 (8%)	8/85 (9%)
Hahn (16)	1979	0/36 (0%)	2/62 (3%)	4/23 (17%)	10/121 (5%)
Wilson (17)	1980	0/86 (0%)	3/87 (3%)	0/18 (0%)	3/191 (2%)
Total pooled across studies		33/484	52/594	56/229	141/1307
Percent positive (95% CI)		6.8% (4.6, 9.0)	8.8% (6.5, 11.1)	24.5% (18.9, 30.1)	10.8% (9.1, 12.5)

NA, not available.

Table 4. Bone scan results by stage of disease, from studies reported after 1980.

1st author (Reference)	Year of report	# patients with positive bone scan/ #patients in study (%)			
		Stage I	Stage II	Stage III	Total
Kunkler (18)	1985	1/66 (2%)	19/256 (7%)	24/143 (17%)	44/465 (9%)
Khansur (19)	1987	0/92 (0%)	4/95 (4%)	24/78 (31%)	28/265 (11%)
Coleman (20)	1988	0/271 (0%)	15/593 (3%)	13/179 (7%)	28/1043 (3%)
Ciatto (21)	1988	1/550 (0.2%)	14/1317 (1%)	6/508 (1%)	21/2375 (1%)
Ahmed (22)	1990	2/80 (3%)	9/226 (4%)	13/83 (16%)	24/389 (6%)
Kennedy (23)	1991	0/13 (0%)	1/60 (2%)	2/11 (18%)	3/84 (4%)
Cox (24)	1992	1/122 (1%)	2/180 (1%)	6/37 (16%)	9/339 (3%)
Brar (25)	1993	0/21 (0%)	2/67 (3%)	2/43 (5%)	4/131 (3%)
Yeh (26)	1995	2/204 (1%)	5/112 (4%)	NA	7/316 (2%)
Total pooled across studies		7/1419	71/2906	90/1082	168/5407
Percent positive (95% CI)		0.5% (0.1, 0.9)	2.4% (1.8, 3.0)	8.3% (6.7, 9.9)	3.1% (2.6, 3.6)

NA, not available.

It is not possible to explain completely the differences in results between patients seen before 1980 and those seen after. In recent years, patients presenting to surgeons have smaller lesions; this would alter the composition of the stage I group by including more women with smaller tumours. In early studies, bone lesions that were called abnormal did not always progress to frank bone metastases and might not be designated malignant if reviewed now. Today, an abnormal bone scan would precipitate plain radiographs and possibly biopsy if there was any doubt about etiology. Nonetheless, both sets of studies show an increase in abnormalities as stage of disease increases. It is important that staging decisions be based on current information, and hence the results from Table 4 should be used for making clinical or policy decisions.

Liver Ultrasound

The liver is less frequently involved by metastatic breast cancer than bone (4,17). Tests to determine liver involvement include physical exam, liver function blood tests, liver scan, liver ultrasound, liver CT, and liver MRI. The evidence available to determine which modality is best is conflicting and this conflict is not completely resolved (1,24,25,27,30-32). Nonetheless, the test currently used most frequently for staging is ultrasound.

Table 5 summarizes the results of four studies of baseline ultrasound of the liver, tabulated by stage of disease. All of these were reported after 1980. Data were collected retrospectively in two studies (21,28) and prospectively in two (24,27). Liver scans were performed before surgery in two studies (21,27), after surgery in one (28) and before or after in the fourth (24). Based on these data, the chance of an abnormal test appears to be even lower than that observed in the bone scan studies.

Depending on how strictly one defines abnormalities in the liver, the false-positive rate may vary from 33% (2 of 6) up to 52% (11 of 21) (28) and is probably higher than one can expect currently. However, there are many benign incidental findings with routine ultrasound; in

one study, 100 benign findings were noted among 346 patients (24).

There were no clear data exploring a relationship between liver ultrasound results and normal versus abnormal liver function tests.

Table 5. Liver ultrasound results by stage of disease at diagnosis of breast cancer.

1st author (Reference)	Year of report	# patients with positive liver scan/ #patients in study (%)			
		Stage I	Stage II	Stage III	Total
Ciatto (21)	1988	0/132 (0%)	1/462 (0.2%)	1/194 (0.5%)	2/788 (0.3%)
Clark (27)	1988	0/110 (0%)	0/86 (0%)	1/24 (4.2%)	1/220 (0.5%)
Glynne-Jones (28)	1991	0/54 (0%)	3/167 (1.8%)	2/50 (4.0%)	5/271 (1.8%)
Cox (24)	1992	0/127 (0%)	0/182 (0%)	2/37 (5.4%)	2/346 (0.6%)
Total pooled across studies		0/423	4/897	6/305	10/1625
Percent positive (95% CI)		0% 0.0	0.4% (0.0, 0.8)	2.0% (0.4, 3.6)	0.6% (0.2, 1.0)

Chest Radiograph

The lung, although not as common a site as bone for the development of metastatic disease, is still routinely assessed in staging the breast cancer patient. Only two studies have reported chest radiograph results by stage of disease, and their results are shown in Table 6. Both studies collected data retrospectively; chest radiographs were performed before surgery in one study (21) and after surgery in the other (28).

As for the other staging modalities, chest radiography was shown to have an appreciable false-positive rate of 23% (3 of 13) when equivocal results were considered. However, when stricter criteria were used for eight positive cases, none were false positives (28).

Table 6. Chest radiograph by stage of disease at diagnosis of breast cancer.

1st author (Reference)	Year of report	# patients with positive chest radiograph/ #patients in study (%)			
		Stage I	Stage II	Stage III	Total
Ciatto (21)	1988	1/873 (0.1%)	3/1943(0.2%)	7/682 (1.0%)	11/3498(0.3%)
Glynne-Jones (28)	1991	0/64 (0%)	2/240 (0.8%)	6/82 (7.3%)	8/386 (2.1%)
Total pooled across studies		1/937	5/2183	13/764	19/3884
Percent positive (95% CI)		0.1% (0, 0.3)	0.2% (0, 0.4)	1.7% (0.8, 2.6)	0.5% (0.3, 0.7)

V. INTERPRETIVE SUMMARY

There have been many studies assessing the value of bone scan, liver ultrasound and chest radiograph in breast cancer staging. Studies where results were reported by conventional TNM stage have all been reviewed for this practice guideline. Those reported up to 1980 tended to demonstrate rates of positive bone scans that were higher than the rates found by studies reported after 1980. The yield of baseline testing increases with stage of disease but overall is very low for all three sites of metastases in asymptomatic patients. The pooled detection rates (i.e. the proportion of tests that were positive for metastases) in stage I breast cancer, from

studies published after 1980, were 0.5% for bone scan, 0% for liver ultrasound and 0.1% for chest radiograph. In women with stage II disease, 2.4% of bone scans, 0.4% of liver ultrasounds and 0.2% of chest radiographs detected metastases. Rates of positive tests for stage III disease were 8.3%, 2.0% and 1.7% for bone scan, liver ultrasound and chest radiograph, respectively. The strength of the available evidence lies not in study design, which in some cases is quite weak, but principally in the number of patients that have been studied: 5407 patients with bone scans, 1625 with liver ultrasounds and 3884 with chest x-rays and the corresponding narrow confidence intervals for the estimates of detection rate.

VI. ONGOING TRIALS

The Breast Cancer DSG is not aware of any ongoing, relevant randomized trials of baseline staging in primary breast cancer.

VII. BREAST CANCER DISEASE SITE GROUP CONSENSUS PROCESS

A poll of DSG members indicated that baseline testing (bone scan, liver ultrasound and chest radiograph) is currently being performed at diagnosis on virtually every woman with operable invasive breast cancer in Ontario. In some hospitals, even women with intraductal cancers have these tests performed. These tests may be repeated after referral to secondary or tertiary treatment centres. In some hospitals, staging tests may be performed prior to surgery; however, given that complete tumour and axillary-nodal staging cannot be known until after surgery, it would be more logical to perform the tests, if needed, after surgery. The systematic overview of the evidence summarized in this practice guideline demonstrates that these tests rarely detect metastases in asymptomatic women. However, there are a significant number of false-positive test results that oblige the physician to perform other more invasive tests. After reviewing this evidence, the Breast Cancer DSG agreed that it was time to rethink the strategy for baseline testing in the "well" operable woman with breast cancer. The DSG considered baseline testing to be a separate issue from the use of these tests as part of follow-up assessment after treatment for breast cancer, which has been dealt with in a published clinical practice guideline (33).

There are several arguments made in support of these tests: women may demand them; there may be medical-legal issues; doctors feel comfortable ordering them; and clearly there are certain subsets of patients that require them. Nonetheless, there are reasons for abandoning the routine use of these tests: the prevalence of metastatic disease is very low in early-stage disease; the tests are expensive, time consuming and anxiety provoking; women are being diagnosed at much earlier stages of disease than in the past; and finally, metastatic disease is incurable. Currently, the goal of treatment for metastatic disease is palliation. One of the main concerns resulting from not doing baseline staging tests is that a patient could be incorrectly classified, so that a woman thought to have stage I or II disease might in fact have stage IV (metastatic) disease. In this case, the woman might be treated inappropriately. The DSG agreed that while this type of error in staging would clearly be an unfortunate event, its occurrence would be relatively rare. Furthermore, such an error would not deny patients potentially curative treatments.

The Breast Cancer DSG has reviewed the research results summarized in this report in detail. Evidence from studies reported after 1980 was used as the basis for the draft recommendations because it was considered more relevant to current practice than was evidence from earlier studies. DSG members felt that tests that detected metastases in less than one percent of patients and also resulted in a significant number of false-positives-were not clinically useful. Where to place the cut-off for detection rate was a subjective decision, but after discussion at a DSG meeting, the members agreed on one percent.

There were several areas where decision-making was easier than others. In stage I patients, where the yield for all tests was less than 1%, it seems appropriate to recommend the

elimination of routine testing. Although studies of staging have not been performed in women with intraductal disease, there is good reason to assume that the yield from staging tests would be even less than in stage I cases. For this reason, the DSG recommends the elimination of staging tests in this group. Among stage III patients, the proportion of abnormal tests was higher, exceeding 1% for all three tests. In this group, the consensus was that the tests should be retained.

The longest discussion by the DSG concerned the use of staging tests in women with stage II breast cancer. The yield of positive results in this group was 2% for bone scan and less than 1% for ultrasound and chest radiograph. A good case could be made for retaining bone scanning and eliminating liver ultrasound and chest radiograph in this group. The DSG considered the possibility of dividing the stage II group according to size of tumour or number of positive lymph nodes (<4 versus \geq 4 positive nodes). This approach was based on the assumption that risk might vary across the range of stage II patients. For example, a larger number of positive nodes could be associated with a higher likelihood of detecting metastases with staging tests. However, data were not available to answer this question.

Finally, some discussion occurred concerning patients who, because of co-morbid illness, age or personal preference, would not be candidates for chemotherapy but would either be treated with tamoxifen or receive no further treatment after surgery (with or without radiotherapy). Because one of the main purposes of staging is to rule out distant disease that would render the patient incurable with conventional therapy, the DSG did not recommend the use of baseline staging tests in this group of patients, provided they were asymptomatic. In asymptomatic patients where the decision to use tamoxifen or hormone therapy, or to undergo no further treatment has already been made, there seems to be little need to perform staging tests, as the results would not change treatment.

The DSG discussed what other tests should be performed at the time of diagnosis. Although a review of the literature related to this topic was beyond the scope of the practice guideline, the DSG easily reached consensus on the following recommendations: in women with newly diagnosed breast cancer that has been resected, baseline testing should consist of a careful history, physical examination, complete blood count and liver function, serum calcium and renal function tests. Other specific tests may be ordered to assess abnormalities detected by the history, physical exam or laboratory tests. These tests will help the clinician decide whether further tests or imaging are needed. They will also help determine which patients can tolerate chemotherapy.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence described above, the Breast Cancer DSG drafted the following recommendations:

Target population

The following recommendations apply to women with newly diagnosed breast cancer that has been resected, who have no symptoms or signs of metastases.

Draft Recommendations

- In women with intraductal and pathological stage I tumours, chest radiograph, bone scan and liver ultrasound are not indicated routinely.
- In women who have pathological stage II tumours, a bone scan should be ordered routinely. As pathologic confirmation of stage is required, this test should be ordered after surgery. Ultrasound of the liver and chest radiograph are not indicated routinely in this group.

- In women with pathological stage III tumours, routine bone scan, liver ultrasound and chest radiograph should be performed postoperatively.
- In asymptomatic patients who have undergone surgery for their breast cancer and where the treatment options are restricted to tamoxifen or no further treatment because of age or other factors, the use of routine staging should be discouraged.

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

In June 1999, practitioner feedback was obtained through a mailed survey of 147 practitioners in Ontario (48 medical oncologists, 39 radiation oncologists, 44 surgeons and 16 diagnostic radiologists). The survey consisted of 20 questions about the quality of the practice-guideline-in-progress report and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (postcard) and four weeks (complete package mailed again). The results of the survey have been reviewed by the Breast Cancer DSG.

Results

Key results of the practitioner feedback survey are summarized below in Table 7. Ninety-two (63%) questionnaires were returned. Seventy-one (43%) respondents indicated that they are responsible for the care of patients for whom the practice-guideline-in-progress report is relevant. Two respondents indicated that they were unsure, three left the question blank and one answered no but completed the remaining items, to give a total of 77 completed questionnaires. Forty-one respondents (45%) provided written comments.

Table 7: Responses to eight key items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear.	75 (97%)	2 (3%)	0
There is a need for a clinical practice guideline on this topic.	67 (87%)	6 (8%)	4 (5%)
The literature search is relevant and complete.	68 (90%)	4 (5%)	2 (3%)
The results of the trials described in the report are interpreted according to my understanding of the data.	68 (91%)	4 (5%)	3 (4%)
The draft recommendations in this report are clear.	70 (92%)	3 (4%)	3 (4%)
I agree with the draft recommendations as stated.	55 (74%)	8 (11%)	11 (15%)
This report should be approved as a practice guideline.	55 (75%)	7 (10%)	11 (15%)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Very likely or likely	Unsure	Unlikely or not at all likely
	54 (74%)	12 (16%)	7 (10%)

There was some variation among the specialty groups surveyed. Sixty percent of medical oncologists, 75% of radiation oncologists and 92% of surgeons agreed with the draft recommendations as stated. Only three radiologists completed the survey; two of these three agreed with the recommendations.

Main Points Made as Comments

1. Several respondents commented on the recommendations for baseline staging tests in women with stage II disease. Some questioned the need for bone scans in stage II patients when the yield is only 2-3%. Others were reluctant to discontinue routine chest radiographs and liver ultrasounds in this group, especially in patients who may have a higher probability of metastatic disease (e.g., patients with four or more positive lymph nodes).
2. Some practitioners were concerned about not performing imaging tests in older patients and those for whom chemotherapy is not recommended.
3. Practitioners asked if there is evidence to support the routine use of liver function, serum calcium and renal function tests at baseline.
4. A guideline on the use of routine imaging in follow-up was requested.
5. Some clinicians felt that the practice guideline was too rigid and dictated clinical judgement.

Modifications/Actions

1. Unfortunately, the evidence available does not address the differential value of the staging tests among subgroups of stage II patients. A qualifying statement was added to the recommendations for stage II patients suggesting that a chest radiograph and liver ultrasound could be considered for patients with four or more positive lymph nodes. A recommendation that the association between nodal status and the results of baseline staging tests be studied prospectively has also been added to the guideline report under the heading Future Research.
2. Further explanation for this recommendation was added to the DSG Consensus section of the guideline report. A statement, that one of the main purposes of staging is to rule out distant disease that would render the patient incurable with conventional therapy, was added to the Choice of Topic & Rationale section.
3. The issue of baseline blood tests was not directly addressed by the practice guideline. However, it was discussed by the DSG during the development of the guideline and some consensus-based recommendations were included in the discussion section of the practice-guideline-in-progress report. Following practitioner feedback, the rationale for baseline blood tests was added to the Disease Site Group Consensus section of the guideline report.
4. The Breast Cancer DSG endorses the recommendation of the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer that routine radiographic investigations should not be carried out for the purpose of detecting distant metastases during follow-up after treatment for breast cancer (33).
5. The DSG feels that the recommendations are consistent with the evidence from the literature, but recognizes that some patients and physicians may choose to use a different approach to staging than is suggested by the guideline. In order to make it clear that the practice guideline is intended to assist rather than to dictate treatment decisions, the language in the recommendations was modified from "should be performed/ordered" to "is recommended".

IX. FUTURE RESEARCH

Future studies should focus on the relationship between nodal status and the rates of detection of metastases by routine baseline testing with bone scan, liver ultrasound and chest radiograph.

X. PRACTICE GUIDELINE

Target Population

The following recommendations apply to women with newly diagnosed breast cancer who have undergone surgical resection and who have no symptoms, physical signs or biomedical evidence of metastases.

Recommendations

- 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.
- 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.

XI. JOURNAL REFERENCE

Myers RE, Johnston M, Pritchard K, Levine M, Oliver T and the Breast Cancer Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative. Baseline staging tests in primary breast cancer: a practice guideline. CMAJ 2001 May 15;164(10):1439-44.

XII. ACKNOWLEDGMENTS

The Breast Cancer Disease Site Group would like to thank Robert Myers for taking the lead in drafting, revising and updating this practice guideline, with the assistance of Mary Johnston.

For a complete list of the Breast Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit our web site at:
http://www.cancercare.on.ca/access_PEBC.htm.

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Appendix 1. Stage grouping for breast cancer.

TNM STAGING

Primary Tumor (T)

- Tx Primary tumor cannot be assessed
- To No evidence of primary tumor
- Tis Carcinoma in situ: Intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no tumor
- T1 Tumor 2 cm or less in greatest dimension
 - T1mic Microinvasion 0.1 cm or less in greatest dimension
 - T1a More than 0.1 cm but not more than 0.5 cm or less in greatest dimension
 - T1b More than 0.5 cm but not more than 1 cm in greatest dimension
 - T1c More than 1 cm but not more than 2 cm in greatest dimension
- T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension
- T3 Tumor more than 5 cm in greatest dimension
- T4 Tumor of any size with direct extension to chest wall or skin
 - T4a Extension to chest wall
 - T4b Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to 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)
- No No regional lymph node metastasis
- N1 Metastasis to movable ipsilateral axillary lymph node(s)
- N2 Metastasis to ipsilateral axillary lymph node(s) fixed to one another or to other structures
- N3 Metastasis to ipsilateral internal mammary lymph node(s)

Distant Metastasis (M)

- Mx Presence of distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis (includes metastasis to ipsilateral supraclavicular lymph nodes)

STAGE GROUPING

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

Source: American Joint Committee on Cancer. AJCC Cancer Staging Manual, 5th edition, 1997.