CANCERCare
A PROGRAM OF EASTERN HEALTH

Clinical Practice Guidelines - Breast Disease Site

Guideline Title:	Staging of Primary Breast Cancer	**Date:**	**(O):**	July 31, 2011
			(R):	
Tumor Group:	Breast Disease Site Group	**Page:**		1 of 9
Issuing Authority:	Dr. Kara Laing Clinical Chief, Cancer Care Program	**Date Signed:**		May 23, 2012
Adapted From:	Alberta Health Services "Staging investigations for asymptomatic and newly diagnosed breast cancer" guideline, April 2011 (20).			

Introduction:

Prior to definitive surgery, patients with newly diagnosed malignant breast masses often undergo a series of investigations of the breast and axilla, including bilateral mammography, biopsy, ultrasound (US) and when indicated, magnetic resonance imaging (MRI). Frequently, if cancer is diagnosed, further treatment is required post-operatively in the form of systemic therapy or radiation.

The American Joint Committee on Cancer (AJCC) system is a strategy for grouping patients into prognostic stages ranging from Stage I to IV. Stage IV breast cancer is defined as the metastatic spread of invasive cancer beyond the breast and nearby lymph nodes to other organs of the body (1). The most common sites of metastases from a malignant breast primary include bone, liver, lung and brain. Metastases may be suspected in patients with symptoms, abnormal laboratory or staging investigations. A diagnosis of stage IV disease will change the prognosis, therapeutic goals, and potentially the treatment itself (2).

The benefits of staging newly diagnosed patients with breast cancer would include providing the patient with a more detailed discussion on prognosis, allowing the introduction of appropriate palliative care measures at an earlier opportunity, and improving the ability to individualize treatment regimens. For example, more aggressive chemotherapy could be reserved for when the aim is cure while a more balanced, quality-of-life approach can be used for those with metastatic disease (2). The downside of performing staging investigations can include inconvenience to the patient, inappropriate use of limited health care resources, risk of false positives resulting in further investigations (including invasive procedures such as biopsy), and patient anxiety. The question arises then, to what extent should physicians look for occult metastatic disease in asymptomatic patients recently diagnosed with breast cancer?

Questions:

1. Do all patients with early stage breast cancer require staging investigations?
2. What are the recommendations for the use of staging investigations for patients with primary breast cancer within the provincial cancer care program?

Target Population:

These recommendations apply to asymptomatic patients, with a newly diagnosed primary cancer of the breast, who have undergone surgical resection.

Supporting Evidence:

Currently in Newfoundland and Labrador, there are no provincial guidelines for referring physicians (i.e. family physicians, surgeons) to follow when ordering staging investigations in patients with newly diagnosed breast cancer. Patients may present to the Oncology clinic without staging investigations, which could lead to delays in diagnosis and subsequent treatment. Conversely, patients may also arrive with investigations performed which were not indicated.

Several studies, including one completed at our own center, have consistently found that in the absence of symptoms, routinely staging certain subgroups of patients results in low yield of discovery of metastatic disease (3-8). Much of the data collected from these clinical studies are retrospective in nature, which from a methodological point of view, is considered to be weaker evidence in comparison to prospective trials (9). Traditional baseline staging for breast cancer in our province has included bone scan and computed tomography (CT) scan of chest, abdomen and frequently pelvis. Detecting metastatic disease during baseline staging is highly dependent on pathological stage and therefore, baseline staging should be performed in accordance with the AJCC classification system (1,10-14).

Bone scanning with technetium-99m should be performed as baseline staging for all patients with node positive breast cancer. A systematic review by Cancer Care Ontario (CCO) demonstrated that 0.5%, 2.4% and 8.3% of patients in stages I, II, III respectively, had bone metastases on staging bone scan (15). This group reasoned that a test which detected metastases in less than 1% of patients was not clinically useful especially when it also had a significant false-positive rate. Therefore, they conclude that post-operative bone scans should be reserved for patients with pathological stage II or III breast cancers and not for those with “insitu or stage I carcinomas”. We agree in part with these recommendations, however, since some studies show that bone scans are not justified in patients with stage I or II breast cancers in the absence of signs or symptoms of metastatic disease, we have elected to perform bone scans in stage II patients with node positive disease only (16).

Imaging for lung and liver metastases should be performed in all stage III patients, according to the clinical practice guidelines that were reviewed for this guideline (15,17-20). A pooled analysis from the CCO guideline showed that the rate of lung metastases on chest x-ray (CXR) in stage III patients was 1.7%, and the rate of liver metastases on liver US was 2.0%. However, controversy exists for stage II patients which consists of both node positive and node negative

tumours (6,21-24). Guidelines from Alberta Health Services (AHS) and the European Society of Medical Oncology (ESMO) suggest that lung and liver imaging in the stage II cohort is optional, while CCO does not recommend any imaging of the liver and lung in this group (15,18,20). Many studies have shown very low rates of liver and lung metastases detected by CXR and liver US, however very few have studied the detection rate of CT scans in this setting. One expert opinion notes that staging in theory, should only be performed on patients with large tumors or multiple positive nodes, while in practice it would be reasonable to stage patients who have stage III or high-risk stage II disease as well (25). For the stage II cohort, we recommend performing staging investigations in the lymph node positive patients only. This recommendation is based on the heterogeneity of the stage II group, retrospective nature of the evidence and the uncertainty among our own disease site team members and other expert organizations regarding the role of performing baseline investigations in stage II patients with chest and liver imaging. We will continue to monitor for new data on this cohort.

A study from Memorial Sloan-Kettering Institute assessed the use of pelvic CT in staging and found the yield for metastatic disease was extremely small at 0.5%, and prompted the performance of additional non-relevant testing (10). Therefore, staging of the pelvis in patients with breast cancer is not recommended unless the patient is symptomatic.

Several studies have looked at the role of positron emission tomography (PET) in breast cancer staging (26-28). At present, there is no data to indicate a use for routine baseline PET staging in primary breast cancer and limited data which suggests that it best serve as a confirmatory test (27).

Based on emerging evidence that some biological subtypes of breast cancer may behave more aggressively at presentation, oncologists may elect to stage some node negative patients based on pathological and patient characteristics (i.e. triple negative tumours).

Recommendations:

The following recommendations of the Eastern Health Breast Disease Site Group apply to patients with newly diagnosed stage I-III breast cancer, who have completed surgery, are asymptomatic, and have no physical findings or laboratory abnormalities to suggest metastatic disease.

- All patients should undergo history and physical exam, complete blood count, renal and liver function tests, bilateral mammography, and determination of estrogen/progesterone receptor (ER/PR) and human epidermal growth factor receptor (HER2) status of the tumor.
- Staging investigations should be performed postoperatively according to pathological stage.
- No staging investigations are necessary for patients with *in situ* carcinomas or T1-2, node negative disease.
- A baseline bone scan and CT scan of chest/abdomen should be performed in all patients with node positive disease.
- Patients with documented contrast allergy or other contraindications to intravenous contrast should have an unenhanced CT scan of the chest and abdomen, and an US of the liver.
- Routine use of tumor markers or PET scanning as part of baseline staging is not recommended at this time.

When staging investigations are recommended, it would be most beneficial if these were ordered prior to the patient's visit to the oncologist. Ordering the recommended investigations is sufficient – patients' referral to an oncologist should not be delayed while awaiting the results.
If the patient has symptoms of metastatic disease (i.e. abdominal pain, dyspnea), physical findings (i.e. abdominal mass) or abnormal laboratory results (i.e. liver function anomalies), then it is reasonable to stage these patients accordingly.

Note: These guidelines do not apply to patients with locally advanced breast cancer (i.e. T4 tumors, inflammatory breast cancer) who may require neoadjuvant therapy. These patients are considered to have a higher risk of metastases and should be staged preoperatively with a bone scan and CT of chest and abdomen (2,29).

Search Strategy:

Literature searches were conducted in PubMed, Embase, and the Cochrane Library, using keywords "breast" AND "neoplasms" AND "baseline staging tests", as well as an extensive manual search of the reference lists of available literature articles. Guideline searches were also carried out on the websites of the world's most highly respected cancer organizations and agencies. All selected literature articles and source guidelines were in English and dated after the year 2000 (unless the selection was an earlier landmark study) up to July 2011. The inclusion/exclusion process consisted of selecting guidelines from reputable cancer organizations with preference given to those from Canadian sources where possible. Eight source guidelines were identified and conformed to our search criteria, from which five were selected due to currency, quality of content and/or were Canadian in origin (15,17-20,30-32).

The five identified source guidelines (15,17-20) were put through the ADAPTE process (33) with an AGREE II assessment (34), and the AHS "staging investigations for asymptomatic and newly diagnosed breast cancer" guideline was chosen to be adapted for use in our guideline (20). The AHS guideline was selected as the optimal choice due to its applicability, quality and currency of content.

There has been much debate but no consensus on the 'grading of evidence' in Canada. Presently, Canadian experts in the field of guideline development are involved in an ongoing in-depth analysis of the functionality of grading. Until such time as a report is released of their findings, and a consensus reached on whether to assign a grade of recommendation to a guideline, this group has decided to forgo the use of grading.

No competing or conflicts of interest were declared.

Disclaimer:

These guidelines are a statement of consensus of the Breast Disease Site Group regarding their views of currently accepted approaches to diagnosis and treatment. Any clinician seeking to apply or consult the guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

Contact Information:

For more information on this guideline, please contact Dr. Melanie Seal MD FRCPC, Dr. H. Bliss Murphy Cancer Center, St. John's, NL; Telephone 709-777-8515. For access to any of our guidelines, please visit our Cancer Care Program website at www.easternhealth.ca

Literature Support:

1. Edge SB, Byrd DR, et al. AJCC Cancer Staging Manual, 7th ed. New York, NY:Springer, 2010, pp.347-376.
2. Al-Husaini H, Amir E, et al. Prevalence of overt metastases in locally advanced breast cancer. Clin Oncol. 2008;20:340-344.
3. Samant R & Ganguly P. Staging investigations in patients with breast cancer: The role of bone scans and liver imaging. Arch Surg. May 1999;134:551-553.
4. Ravaioli A, Pasini G, et al. Staging of breast cancer: New recommended standard procedures. Breast Cancer Res Treat. 2002;72:53-60.
5. Gerber B, Seitz E, et al. Perioperative screening for metastatic disease is not indicated in patients with primary breast cancer and no clinical signs of tumor spread. Breast Cancer Res Treat. 2003;82:29-37.
6. Schneider C, Fehr MK, et al. Frequency and distribution pattern of distant metastases in breast cancer patients at the time of primary presentation. Arch Gynecol Obstet. 2003;269:9-12.
7. Puglisi F, Follador A, et al. Baseline staging tests after a new diagnosis of breast cancer: Further evidence of their limited indication. Ann Oncol. 2005;16:263-266.
8. Barrett T, Bowden DJ, et al. Radiological staging in breast cancer: Which asymptomatic patients to image and how. Br J Cancer. 2009;101(9):1522-1528.
9. Tassinari D, Sartori S, et al. Staging of breast cancer: Is the evidence so evident? Ann Oncol. 2001;12:1653.
10. Drotman MB, Machnicki SC, et al. Breast cancer: Assessing the use of routine pelvic CT in patient evaluation. AJR. June 2001;176:1433-1436.
11. Lee JE, Park S, et al. The clinical use of staging bone scan in patients with breast carcinoma: Reevaluation by the 2003 American Joint Committee on cancer staging system. Cancer. 2005;104(3):499-503.
12. Kasem AR, Desai A, et al. Bone scan and liver ultrasound scan in the preoperative staging for primary breast cancer. Breast J. 2006;12(6):544-548.
13. Puglisi F, Andreetta C, et al. Bone scan for baseline staging in invasive breast cancer at the time of primary presentation. Breast Care. 2007;2(6):358-364.
14. Roberts CC, Daffner RH, et al. ACR appropriateness criteria on metastatic bone disease. J Am Coll Radiol. 2010;7(6):400-409.
15. Myers RE, Johnston M, et al 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. 2001(reviewed 2003;and Nov 2011). www.cancercare.on.ca
16. Dillman RO & Chico S. Radiologic tests after a new diagnosis of breast cancer. Effective Clinical Practice. 2000;3(1):1-6.
17. NZGG . Management of early breast cancer: Evidence-based best practice guideline. New Zealand Guidelines Group. 2009. www.nzgg.org.nz

18. Aebi S, Davidson T, et al and the ESMO (European Society of Medical Oncology) Guidelines Working Group. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010; 21(suppl 5):v9-v14.
19. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Breast cancer. 2011. www.nccn.com
20. Alberta Health Services. Staging investigations for asymptomatic and newly diagnosed breast cancer. April 2011. www.albertahealthservices.ca
21. Ravaioli A, Tassinari D, et al. Staging of breast cancer: What standards should be used in research and clinical practice? Ann Oncol. 1998;9:1173-1177.
22. Samur M, Bozcuk HS, et al. Reevaluation of baseline staging tests in breast cancer: What should be the standard? Turk J Cancer. 2003;33(3):150-153.
23. Bombardieri E, & Gianni L. The choice of the correct imaging modality in breast cancer management. Eur J Nucl Med Mol Imag. 2004;31(Suppl. 1):S179-S186.
24. Müller D, Köhler G, et al. Staging procedures in primary breast cancer. Anticancer Res. 2008;28:2397-2400.
25. Tolaney SM & Winer EP. Follow-up care of patients with breast cancer. Breast. 2007;16(supp.):S45-S50.
26. Carr CE, Conant EF, et al. The impact of FDG PET in the staging of breast cancer. ASCO Annual Meeting Proceedings. J Clin Oncol. 2006 June 20 Supplement;24(18S):530.
27. Shie P, Cardarelli R, et al. Meta-analysis: Comparison of F-18 fluorodeoxyglucose-position emission tomography and bone scintigraphy in the detection of bone metastases in patients with breast cancer. Clin Nucl Med. 2008;33(2):97-101.
28. Fuster D, Duch, et al. Preoperative staging of large primary breast cancer with [18F} Fluorodeoxyglucose positron emission tomography/computed tomography compared with conventional imaging procedures. J Clin Oncol. 2008;26(29):4746-4751.
29. Whitman GJ & Strom EA. Workup and staging of locally advanced breast cancer. Semin Radiat Oncol. 2009;19:211-221.
30. Perry N on behalf of EUSOMA Working Party. Multi-disciplinary aspects of quality assurance in the diagnosis of breast disease. European Society of Breast Cancer Specialists. Revised 2005. www.eusoma.org
31. CCMB. Breast Cancer Referral Guidelines. CancerCare Manitoba. 2005. www.cancercare.mb.ca
32. BCCA. Breast – Staging. Investigations for staging. British Columbia Cancer Agency. 2006. www.bccancer.bc.ca
33. Brouwers M, Browman G, et al. Guideline adaptation: Enhancing efficiency in guideline development and utilization. www.adapte.org
34. Brouwers M, Kho ME, et al for the AGREE Next Steps Consortium. AGREE II: Advancing guideline development, reporting and evaluation in healthcare. Can Med J. 2010.doi : 10.1503/cmaj.090449

Appendix

TNM Staging Tool

Alberta Health Services

CLINICAL PRACTICE GUIDELINE BR-012

APPENDIX A: AMERICAN JOINT COMMITTEE ON CANCER (AJCC) TNM STAGING DEFINITIONS

The following information was reproduced from the AJCC Cancer Staging Manual, 7th Edition (2010).

Primary Tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	DCIS
Tis (LCIS)	LCIS
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
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 nodes metastases
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted OR metastases in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement OR metastases in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases OR metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)

Pathologic (pN)	
pNx	Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically.
Note: ITCs are defined as small clusters of cells ≤0.2 mm, or single tumor cells, or a cluster of <200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by IHC methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.	
pN0(i-)	No regional lymph node metastases histologically, negative IHC
pN0(i+)	Malignant cells in regional lymph node(s) ≤0.2 mm (detected by H&E or IHC including ITC)
pN0(mol-)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
pN0(mol+)	Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases OR metastases in 1-3 axillary lymph nodes AND/OR metastases in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected
pN1mi	Micrometastases (>0.2 mm and/or >200 cells but none >2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis >2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in 4–9 axillary lymph nodes OR metastases in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least 1 tumor deposit >2 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases
pN3	Metastases in ≥10 axillary lymph nodes (at least 1 tumor deposit >2.0 mm) OR metastases in infraclavicular (level III axillary) lymph nodes OR metastases in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes OR metastases in >3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically OR metastases in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in ≥10 axillary lymph nodes (at least 1 tumor deposit >2.0 mm) OR metastases in infraclavicular (level III axillary) lymph nodes
pN3b	Metastases in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes OR metastases in >3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Distant Metastases (M)

M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are ≤0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven >0.2 mm

Anatomic Stage/Prognostic Groups

Stage	*T*	*N*	*M*
0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1mi	M0
	T1	N1mi	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