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Clinical Practice Guidelines - Breast Disease Site

Guideline Title:	Baseline Staging of Primary Breast Cancer	**Date:**	**(O):**	July 31, 2011
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Tumor Group:	Breast Disease Site Group	**Page:**		1 of 19
Issuing Authority:	Dr. Teri Stuckless Clinical Chief, Cancer Care Program	**Date Signed:** Aug 31, 2023		
Adapted From:	Cancer Care Ontario guideline “Baseline staging imaging for distant metastases in women with stage I, II, and III breast cancer”, October 2019 (44).			

Introduction:

Breast cancer is the most diagnosed cancer in Canadian women (1). Establishing prognosis and developing a treatment plan for breast cancer requires an accurate disease staging workup. Fortunately, approximately 82% of patients today are diagnosed at a much earlier stage due mainly to national breast screening programs and a successful education campaign of awareness among the population (1,2). The ever increasing costs of health care have motivated the need for policy initiatives across the country to address value-based care through programs such as Choosing Wisely Canada endorsed in 2014 (3,4). This initiative has addressed practices which are unnecessary for many patients and financially expensive to the healthcare system. Debate does exist however, whether certain subgroups of patients with breast cancer at highest risk of recurrence warrant the use of baseline staging investigations.

Questions:

1. Are baseline imaging investigations necessary for all patients with primary breast cancer?

2. Should biomarker status of primary breast cancer influence the use of baseline investigations recommended for these patients?

3. What are the new recommendations for the use of baseline investigations in patients with primary breast cancer in Newfoundland and Labrador?

Target Population:

These recommendations apply to asymptomatic patients with a newly diagnosed, pathologically confirmed primary cancer of the breast.

Supporting Evidence:

Patients who have been diagnosed with primary breast cancer often undergo loco-regional imaging using bilateral mammography, spot compression views, ultrasonography, and sometimes magnetic resonance imaging (MRI) to determine the extent of local disease prior to surgical resection. Routinely, patients are required to have a history and physical examination and preoperative bloodwork. Following definitive surgery, a detailed pathology report is provided including biomarker testing for estrogen receptors (ER) and progesterone receptors (PR), as well as, human epidermal growth factor receptor 2 (HER2). The American Joint Committee on Cancer (AJCC) 8th ed. staging manual* defines primary breast cancer in terms of the TNM system which highlights the size of the tumor (T), the number of lymph nodes invaded by cancer (N), and whether metastatic spread has been detected (M) (5). This knowledge, in addition to biomarker results, aids oncologists in making individual patient-directed treatment decisions.

Additional baseline staging tests (typically chest radiography, liver ultrasound, and bone scan) were historically ordered for most patients diagnosed with primary breast cancer in an attempt to detect the presence of distant metastatic disease. More recently, computed tomography (CT) of the chest and abdomen has replaced the use of chest x-ray and liver ultrasound while even newer technologies such as positron emission tomography-computed tomography (PET-CT) have also been studied in this setting for their diagnostic and prognostic value. Early studies have indicated that conventional staging investigations reveal a low incidence of metastatic disease in asymptomatic patients diagnosed with early stage breast cancer (6-8). These findings also suggest that there is a significant correlation between an increasing incidence of metastatic spread with increase in pathological tumor size and number of lymph nodes involved. Evidence suggested that baseline staging may be unnecessary in patients having AJCC stage I-II breast cancer and should be reserved for ≥ stage III patients only. A systematic review later confirmed that the metastatic detection rate of baseline staging increased in accordance with stage of disease, with early-stage breast cancer patients (stage I and II) yielding a median rate of 0.2% and 1.2%, respectively while stage III disease had a median rate of 13.9% (9). Though the authors acknowledge that selection bias may have been a factor in some of the smaller studies in this review, there was ‘strong and consistent evidence’ from the larger studies which supported their conclusion that the rate of distant metastases was positively correlated with increasing stage of disease at presentation. This evidence supports the use of baseline staging in all patients having stage III breast cancer.

Inflammatory Breast Cancer

IBC is an aggressive type of breast cancer which is characterized by erythema and edema of the skin, with a ‘peau d’orange’ appearance. Interestingly, the above systematic review also identified patients with inflammatory breast cancer (IBC), a sub-group of the stage III breast cancer population, as having a median distant metastatic detection rate of 39.6% during baseline testing (9). This was also supported by another study, not included in the previous systematic review, which examined metastatic disease patterns during baseline investigations between patients with IBC versus locally advanced, non-inflammatory breast cancer (defined as having a tumor size >5cm) (10). The results suggest that on CT imaging, 26% of patients with IBC had distant metastatic disease at presentation compared to 10% of patients with non-IBC. IBC is typically treated with neoadjuvant systemic therapy and requires a full staging work-up, in

accordance with the criteria set out by all five source guidelines used in developing this guideline (33-37). Overall, there is sufficient evidence to support baseline staging investigations for detection of metastatic disease in patients with IBC, especially if neoadjuvant therapy is being considered. The Eastern Health BDSG is in agreement with this recommendation as outlined in the Eastern Health "*Neoadjuvant Treatment of Breast Cancer*" guideline located on the Eastern Health website (www.easternhealth.ca) under Cancer Care services.

Use of Positron Emission Tomography-Computed Tomography (PET-CT)
In the last decade, research studies (both retrospective and prospective) have examined the utilization of positron emission tomography-computed tomography (PET-CT) as a staging tool for patients with early-stage breast cancer. A review of the evidence by Cancer Care Ontario (CCO) found that in keeping with previous research on anatomic conventional CT imaging, investigations using PET-CT (or functional imaging) have also shown a very low prevalence of asymptomatic distant metastases detected in patients with stage I and II breast cancer. In patients diagnosed with stage III breast cancer, functional PET-CT imaging detected metastases in 26% of cases (35). This evidence, however, has predominantly been based on retrospective data, observational and single institutional studies. The Ontario Clinical Oncology Group has undertaken a prospective, randomized control trial comparing PET-CT imaging to conventional anatomic CT imaging for staging purposes in clinical stage III breast cancer patients who are to receive neoadjuvant systemic therapy with study closure in December 2022 (registration #NCT02751710). The CCO working group has decided to await the results of this study before recommending the choice of imaging modalities for staging purposes as the standard of practice in this subgroup of the breast cancer population. All selected source guidelines indicate that there is no role for the use of PET-CT investigations in patients having stages I-II breast cancer while both American guidelines, NCCN and UTD, state there is also no role for PET-CT scanning in operable stage III breast cancer (33,34). The consensus appears to be that PET-CT is best used in situations where the findings of standard staging studies are equivocal or suspicious. The Eastern Health BDSG has agreed that the routine use of PET-CT in staging breast cancer is not indicated, unless equivocal or suspicious findings are identified on routine staging investigations.

Biomarker Subtypes
Breast cancer is an heterogeneous disease and the probability of survival depends more on the combination of biomarkers than their individual contributions. These biomarker subtypes are based on the presence or absence of ER, PR, and HER2 receptors on the tumor cells. Gene expression profiling studies of breast tumors have identified at least four subtypes: luminal A, luminal B, human epidermal growth factor receptor 2 overamplification (HER2+), and triple negative/basal-like (TN), as seen in Table 1 (11,12). The HER2-positive and TN subtypes tend to have a more aggressive tumor biology. The HER2+ subtype lacks hormone receptors (estrogen and progesterone) which excludes the use of endocrine therapy, such as tamoxifen or aromatase inhibitors. However, targeted therapies aimed at suppressing the HER2 receptors, in addition to chemotherapy have had good success in treating this disease subtype. Historically, patients with TN subtype have chemotherapy alone as the only therapeutic option. Patients with these tumors also tend to have higher mortality and lower survival rates than those with hormone receptor-positive subtypes (13). Recently, new immunotherapy agents have been introduced in both the neoadjuvant and adjuvant setting for TN breast cancers while targeted therapies are also now used in the metastatic setting as well. For a more detailed description of the biomarker subtypes of breast cancer, please refer to the Eastern Health "*Neoadjuvant Treatment of Breast*

Cancer" guideline located on the Eastern Health website (www.easternhealth.ca) under Cancer Care services.

TABLE 1: **Four Molecular Breast Cancer Subtypes**

Subtype	Molecular Markers
Luminal A	Estrogen receptor (ER) strongly positive and progesterone receptor (PR) strongly positive, HER2 negative
Luminal B	ER positive and/or PR positive, HER2 positive or negative
HER2 neu positive	ER negative and PR negative , HER2 positive
Triple Negative/Basal-like	ER negative and PR negative, HER2 negative

Luminal versus HER2-positive versus Triple Negative Breast Cancers
Luminal breast cancers A and B subtypes comprise the largest proportion of breast cancers and are generally considered to have much more favorable disease-free and overall survival, compared to HER2-positive and TN breast cancers. The amplification or overexpression of HER2 receptors have been identified in approximately 20% of all breast cancers. Targeted anti-HER2 therapy, such as trastuzumab is used in conjunction with chemotherapy when warranted. Research findings have consistently shown that the addition of trastuzumab, or other biosimilar agents, provides a 40% improvement in relative disease-free survival (DFS) and a 37% relative improvement in OS, as well as an increase in the 10-year DFS and OS rates (14,15). HER2-positive breast cancer remains a highly aggressive disease with 20% of patients developing recurrence and distant metastases, despite having received adjuvant chemotherapy and targeted therapies (16,17). In addition, approximately 34% of patients having HER2-positive subtype will develop central nervous system (CNS) disease portending a median survival of 11 – 18 months (18). In comparison, only 14% of patients with luminal subtype, metastatic breast cancers will develop brain metastases.

Triple negative (TN) breast cancers, approximately 15 - 20% of all breast cancers, are also highly aggressive with approximately 46% of these patients developing metastases and a five-year mortality rate of 40% (19). Common metastatic sites include the visceral organs such as lung and liver, and nearly half of all patients with advanced TN breast cancer will develop brain metastases with a median survival of 4.9 months (18). Patients diagnosed with TN breast cancers are more often younger women, black, and have a BRCA 1 or BRCA 2 oncogene mutation (19). Patients having either HER2-positive or TN breast cancers are at much higher risk of relapse or death, which indicates that these two subtypes may require further deliberation on the trajectory of diagnostic workup and treatment pathways.

Choosing Wisely Canada
The Institute of Medicine in the US has estimated that 30% of spending in healthcare is redundant and does not add any value to patient care (20). The Choosing Wisely program began in the US and has since been adopted enthusiastically here in Canada. Choosing Wisely Canada is described as "…a campaign designed to help physicians and patients engage in conversations about unnecessary tests, treatments and procedures, and supports physician efforts to help patients make smart and effective choices to ensure high-quality care" (21). In

keeping with the Choosing Wisely Canada campaign, a local study using 2014-2016 data from the Newfoundland and Labrador Cancer Registry examined the practice of cancer screening investigations in patients having metastatic breast cancer (n = 305) (22). The findings suggested that 37.4% of these patients continued to undergo at least 1 screening investigation, with the most common being mammography and Papanicolaou (Pap) testing. Approximately 70% of these unnecessary screening investigations were ordered by the primary care providers. A key point of the campaign is that by adhering to local and national evidence-based guidelines, physicians can reduce unnecessary healthcare expenditure. A Canadian Tri-Society Task Force consisting of medical, radiation, and surgical oncologists convened in 2013 and developed a list of 'Ten low-value or harmful practices that should be avoided in cancer care' (23). It suggested that oncologists avoid ordering tests to look for metastatic disease in asymptomatic patients if there is no realistic expectation that finding early disease can improve survival or quality of life.

Since the introduction of Choosing Wisely, a number of Canadian cancer organizations have developed guidelines to limit unnecessary staging investigations for patients diagnosed with stage I and II breast cancer (35,38-40). In 2021, the Cancer Quality Council of Ontario reported on the number of early-stage breast cancer patients who received at least one imaging test for staging purposes for the years of 2014 to 2018 (24). Despite there being some improvement over this period, approximately 48% of stage I and 71% of stage II breast cancer patients still received at least one staging test. In addition, a recent Alberta study found that almost 30% of patients with ductal carcinoma in situ (DCIS), a pre-invasive disease of the breast, and invasive, early stage breast cancer had at least one imaging test completed for routine staging purposes (25). While many Canadian physicians are aware of, and agree with, existing guidelines on imaging for staging purposes, adherence to these guidelines is inconsistent (26). An Ottawa survey study of breast cancer patients found that the vast majority preferred imaging even when it was against their physician's advice and guideline recommendations (27). Across Canada, more work is necessary to eliminate unnecessary baseline staging investigations for patients with early-stage breast cancer.

Pre-existing Guidelines regarding Staging of Patients with Early-Stage Primary Breast Cancer
North American-based guidelines, including the National Comprehensive Cancer Network (NCCN) and Up-To-Date (UTD), and CCO, maintain that routine imaging for staging purposes is not recommended for patients having newly diagnosed, stage I or II breast cancer in the absence of signs or symptoms suspicious for metastatic disease, regardless of biomarker status (33-35). They suggest staging investigations should be reserved for those with stage III breast cancer or those having signs and symptoms suspicious of metastatic disease. All three of these guidelines stipulate that regardless of tumor biology or biomarker status, no patient with stage I or II breast cancer should undergo baseline staging imaging. The European Society for Medical Oncology (ESMO) and the German Deutsches Arzteblatt International (DAI) agree with these recommendations, however they suggest that biomarker subtype should be considered, arguing that aggressive tumor biology (e.g., HER2+ and TN) is associated with a higher risk of metastases in comparison to the luminal subtypes, and therefore should be eligible for staging investigations (36,37). Conversely, Cancer Care Ontario emphasizes that the role of biomarkers in this setting has not been adequately studied in prospective trials and therefore should not be used in decision-making regarding baseline investigations, regardless of whether the patient may undergo neoadjuvant treatment or not (35).

Baseline Staging for Stage II, HER2-positive/TN Breast Cancer
Two recent studies suggest that the rate of upstaging to M1 during imaging for baseline staging was significant for stage IIB breast cancers (28,29). A retrospective analysis of 685 patients with newly diagnosed, early-stage breast cancer who had undergone radiological staging revealed that distant metastases were detected in 32 patients (4.7%) (28).The univariate analysis showed a statistically significant association with distant metastases for stage IIB disease and pathological lymph node involvement (pN1). For TN and HER2-positive breast cancers, only a trend was noted for an association between subtype and distant metastases, however further subgroup analysis suggested a distant metastatic rate of 14.4% in HER2+ and TN stage IIB patients. The authors agreed that baseline staging of asymptomatic, unselected patients was unwarranted however, there may be subgroups of patients such as those with stage IIB with pN1 disease who may have indications for imaging. Another retrospective study of 370 patients with stage I-III disease found that upstaging in stage IIB to M1 disease was 18.8%, and recommended that distant metastatic investigations should be considered in patients with clinical stage IIB disease or higher (29). Interestingly, a recent study looked at identifying factors which may be predictive of distant metastases in 1377 women with newly diagnosed breast cancer in the UK (30). The findings indicate that patients with tumors >3cm and abnormal axillary nodes (defined as metastatic involvement detected by sampling), had a greater positive predictive value (PPV) for the presence of metastatic disease than patients with one variable alone (PPV 18.8%, OR 4.83, P<0.001, 115 patients). This evidence suggests that baseline investigations of stage II patients may be justified, especially in those having highly aggressive breast cancers.

A retrospective study performed at our own cancer center, the Dr. H. Bliss Murphy Cancer Centre, identified 112 patients who were diagnosed with TN breast cancer over a 3-year period (January 2008 and December 2010) (31). The study looked at the rate of metastatic disease identified during baseline radiographic imaging according to stage of disease and attempted to determine whether baseline investigations were necessary for early-stage breast cancer (stages I-II). The results found that 66% of stage I and 92% of stage II patients received baseline imaging. There was no metastatic disease detected on baseline imaging for patients having stage I disease. Conversely, 12% of the patients with asymptomatic, node-negative stage IIA TN breast cancer and 10.5% with stage IIB disease were found to be positive for metastatic disease on CT imaging. The authors concluded that patients with early-stage breast cancer, especially those with stage I disease, may often have undergone unnecessary baseline imaging. However, for patients with stage II TN breast cancer there appears to be sufficient benefit in performing baseline staging, regardless of the nodal status. The retrospective nature and small sample size of these studies are limitations.

Cancer Care Ontario states that the role of biomarkers should not be used in decision-making regarding staging investigations since it has not been adequately studied in prospective trials, regardless of whether the patient may undergo neoadjuvant treatment or not. Although a large prospective trial may illuminate the role of biomarkers in decision-making regarding baseline staging, the likelihood of such a trial being carried out is low due to competing funding priorities (35). It is important to the Eastern Health BDSG to implement recommendations to help reduce the cost of over-using baseline staging investigations without evidence of meaningful benefit. It is also imperative to our health care system and our patients that metastatic disease not be under-diagnosed at initial work-up. This is especially true of candidates for neoadjuvant therapy

where surgical staging of the primary disease comes after initiation of and potential response to systemic therapy.

To determine whether a patient is a candidate for neoadjuvant therapy, and subsequently will require baseline staging investigations, a referral to a surgeon with a breast specialty or a general surgeon is required. In collaboration with NL representatives of Choosing Wisely Canada, the Eastern Health BDSG looked at ways to improve on the wait times of patients between abnormal mammography and start of systemic therapy, regardless of the approach (neoadjuvant vs adjuvant). One point of concern is the time required to have staging investigations completed if the oncologist had to order them at the time of a patient's first visit. Historically, the standard was that radiation treatment should commence within 12 weeks of detected abnormality while chemotherapy should begin once the patients has healed from their surgical procedure. In response, the Eastern Health BDSG has requested that surgeons order the required staging tests (as outlined in Table 2) after pathological confirmation and inform patients in order to expedite patients' journey through the healthcare system.

The Eastern Health BDSG agrees that in the absence of symptoms of metastatic disease, patients diagnosed with stage I breast cancer do not require baseline staging investigations. However, those with clinical or pathological T3 or lymph node positive breast cancer, including those with IBC, should undergo baseline staging investigations regardless of biomarker status. In addition, all patients who are being considered for neoadjuvant treatment should undergo baseline staging investigations, regardless of biomarker status. All patients should be referred to a surgeon who will assume responsibility for ordering the staging tests. Family physicians, general practitioners, or nurse practitioners can also assume responsibility for ordering baseline staging investigations, as highlighted in Table 2.

Table 2: **Baseline Investigations according to Breast Cancer Stage, Selection Criteria, Indication, and Subtype**

Stage and Indication	**Subtypes**			
	Luminal A	Luminal B	HER2-positive	Triple Negative
Stage I and II • <T3 disease • No positive LN involvement • Not a neoadjuvant candidate	No*	No*	No*	No*
Stage II and III • T3 disease or • Positive LN involvement or • Neoadjuvant candidate	CT Chest & Abdomen Bone Scan	CT Chest & Abdomen Bone Scan	CT Chest & Abdomen Bone Scan	CT Chest & Abdomen Bone Scan
Inflammatory Breast Cancer • Neoadjuvant candidate	CT Chest & Abdomen Bone Scan	CT Chest & Abdomen Bone Scan	CT Chest & Abdomen Bone Scan	CT Chest & Abdomen Bone Scan

**in the absence of symptoms of metastatic disease, these stages would not require baseline investigations.*

Recommendations:

The following are recommendations of the Eastern Health Breast Disease Site Group regarding the use of baseline staging investigations for patients with newly diagnosed stage I-III breast cancer:

- Patients who have been newly diagnosed with stage I disease, and are not candidates for neoadjuvant therapy, **should not** undergo any baseline investigations in the absence of symptoms of distant metastases, regardless of biomarker profile;
- All patients with T3 or lymph node-positive breast cancer, including inflammatory breast cancer, **should** undergo baseline staging (CT scan chest/abdomen and bone scan) regardless of biomarker status;
- All patients being considered for neoadjuvant therapy, including those with inflammatory breast cancer, regardless of biomarker status **should** be referred to a surgeon, who in turn will order baseline staging (CT scan chest/abdomen and bone scan) in accordance with the Eastern

Health "Neoadjuvant Therapy for Breast Cancer" guideline. Family physicians, general practitioners, or nurse practitioners can also order baseline staging;

- There is **no** role for the routine use of PET-CT in patients with stage I – III breast cancer.

Search Strategy:

Literature searches were conducted in PubMed, Embase, and the Cochrane Library, using keywords “baseline staging investigations” AND “breast” AND “neoplasms and/or cancer” 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 from August 1, 2011 (unless the selection was an earlier landmark study) up to June 30, 2022. The inclusion/exclusion process consisted of selecting guidelines from reputable cancer organizations with preference given to those from Canadian sources where possible. Seven source guidelines were identified and conformed to our search criteria (33-39), from which five were selected due to currency, applicability and quality of content (33-37).

The five identified source guidelines (33-37) were put through the ADAPTE process (41) with an AGREE II assessment (42), and the Cancer Care Ontario “Baseline staging imaging for distant metastases in women with stage I, II, and III breast cancer” guideline was chosen to be adapted with modifications for use in our guideline (35). The Cancer Care Ontario guideline was selected as the optimal choice due to its superior AGREE II scores in scope and practice, stakeholder involvement, rigor of development, applicability, and its’ Canadian 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, Medical Oncology, Dr. H. Bliss Murphy Cancer Center, St. John’s, NL; Telephone 709-777-7802. For the complete guideline on this topic or for access to any of our guidelines, please visit our Cancer Care Program website at www.easternhealth.ca

Literature Support:

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Glossary:

AJCC: American Joint Committee on Cancer

CCO: Cancer Care Ontario

CT: computed tomography

DAI: Deutsches Arzteblatt International

DFS: disease-free survival

ER: estrogen receptor

ESMO: European Society for Medical Oncology

HER2 neu: human epidermal growth factor receptor

HER2+: over-amplification of human epidermal growth factor receptor

IBC: inflammatory breast cancer

MRI: magnetic resonance imaging

NCCN: National Comprehensive Cancer Network

OS: overall survival

PET-CT: positron emission tomography-computed tomography

PR: progesterone receptor

TN: triple negative

TNM: tumor, lymph nodes, metastases

UTD: Up-To-Date

Appendix:

AJCC Breast Cancer Staging

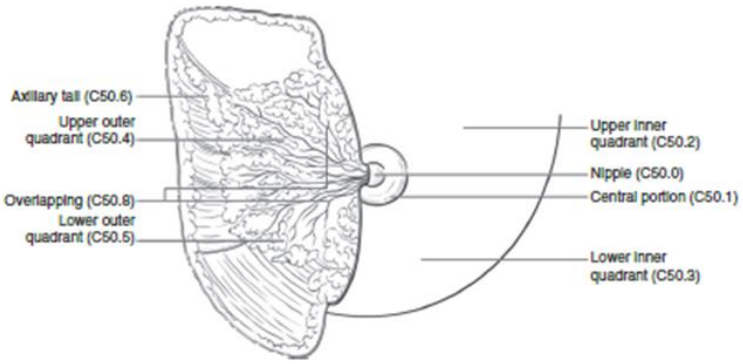

Fig. 48.1 Anatomic sites and subsites of the breast

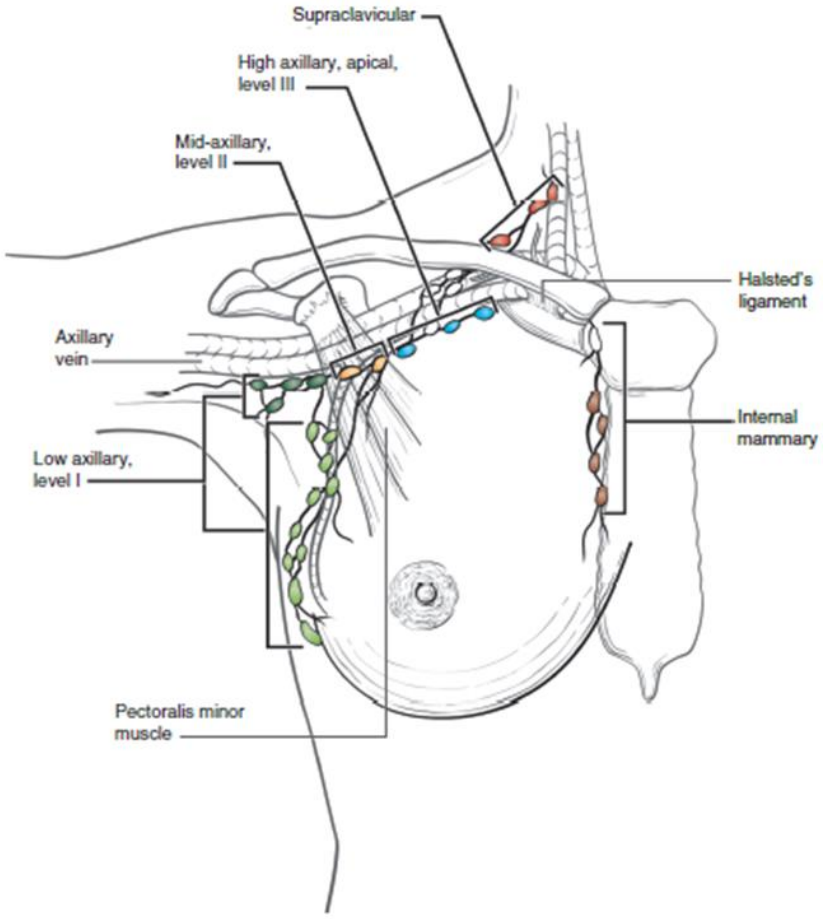

Fig. 48.2 Schematic diagram of the breast and regional lymph nodes

DEFINITIONS OF AJCC TNM

Definition of Primary Tumor (T) – Clinical and Pathological

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)*	Ductal carcinoma *in situ*
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS) 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 (round any measurement >1.0–1.9 mm to 2 mm).
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 macroscopic nodules); invasion of the dermis alone does not qualify as T4
T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4
T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma (see section "Rules for Classification")

**Note:* Lobular carcinoma *in situ* (LCIS) is a benign entity and is removed from TNM staging in the *AJCC Cancer Staging Manual, 8th Edition.*

Definition of Regional Lymph Nodes – Clinical (cN)

cN Category	cN Criteria
cNX*	Regional lymph nodes cannot be assessed (e.g., previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral Level I, II axillary lymph node(s)
cN1mi**	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
cN2	Metastases in ipsilateral Level I, II axillary lymph nodes that are clinically fixed or matted;
	or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN2a	Metastases in ipsilateral Level I, II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement;
	or in ipsilateral internal mammary lymph node(s) with 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
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or fine needle aspiration/core needle biopsy respectively.
*The cNX category is used sparingly in cases where regional lymph nodes have previously been surgically removed or where there is no documentation of physical examination of the axilla.
**cN1mi is rarely used but may be appropriate in cases where sentinel node biopsy is performed before tumor resection, most likely to occur in cases treated with neoadjuvant therapy.

Definition of Regional Lymph Nodes – Pathological (pN)

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed (e.g., not removed for pathological study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph node(s)
pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy
pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
pN1c	pN1a and pN1b combined
pN2	Metastases in 4–9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)

pN Category	pN Criteria
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes
pN3	Metastases in 10 or more axillary lymph nodes;
	or in infraclavicular (Level III axillary) lymph nodes;
	or positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive Level I, II axillary lymph nodes;
	or in more than three axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes;
	or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm);
	or metastases to the infraclavicular (Level III axillary lymph) nodes
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging);
	or pN2a in the presence of pN1b
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or FNA/core needle biopsy respectively, with NO further resection of nodes

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No clinical or radiographic evidence of distant metastases*
cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits no larger than 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases
cM1	Distant metastases detected by clinical and radiographic means
pM1	Any histologically proven metastases in distant organs; or if in non-regional nodes, metastases greater than 0.2 mm

*Note that imaging studies are not required to assign the cM0 category

AJCC ANATOMIC AND PROGNOSTIC STAGE GROUPS

There are three stage group tables: The Anatomic Stage Group table, the Clinical Prognostic Stage Group table and the Pathological Prognostic Stage Group table. Cancer registries and clinicians in the United States must use the Clinical and Pathological Prognostic Stage Group tables for reporting. It is expected that grade, HER2, ER and PR are performed and reported on all cases of invasive cancer in the United States.

Clinical prognostic stage should be recorded on all patients. Pathological prognostic stage should be recorded for patients who have surgery as initial treatment and therefore have pathological T and N information. Patients treated with neoadjuvant therapy should have clnical prognostic stage and the observed degree of response to treatment recorded, but are not assigned pathological prognostic stage.

The Anatomic Stage Group table should only be used in regions of the world where tumor grading and/or biomarker testing for HER2, ER and PR are not routinely available. For worldwide comparison, the Anatomic Stage Group can be back-calculated from U.S. registries from the recorded T, N, and M categories.

AJCC Anatomic Stage Groups

The Anatomic Stage Group table should only be used in global regions where biomarker tests are not routinely available.

Cancer registries in the U.S. must use the Clinical and Pathological Prognostic Stage Group tables for case reporting.

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T0	N2	M0	IIIA
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

Notes:

1. T1 includes T1mi.
2. T0 and T1 tumors with nodal micrometastases (N1mi) are staged as Stage IB.
3. T2, T3, and T4 tumors with nodal micrometastases (N1mi) are staged using the N1 category.
4. M0 includes M0(i+).
5. The designation pM0 is not valid; any M0 is clinical.
6. If a patient presents with M1 disease prior to neoadjuvant systemic therapy, the stage is Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
7. Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided the studies are performed within 4 months of diagnosis in the absence of disease progression, and provided the patient has not received neoadjuvant therapy.
8. Staging following neoadjuvant therapy is denoted with a "yc" or "yp" prefix to the T and N classification. There is no anatomic stage group assigned if there is a complete pathological response (pCR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T0 N1** M0 T1* N1** M0 T2 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
	G3	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T2 N1*** M0 T3 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIB
	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1*** M0 T3 N2 M0	G1	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	G2	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	G3	Positive	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T4 N0 M0 T4 N1*** M0 T4 N2 M0 Any T N3 M0	G1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
	G2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
	G3	Positive	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIC
			Negative	Positive	IIIC
				Negative	IIIC

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
Any T Any N M1	Any	Any	Any	Any	IV

*T1 Includes T1mi.
**N1 does not include N1mi. T1 N1mi M0 and T0 N1mi M0 cancers are included for prognostic staging with T1 N0 M0 cancers of the same prognostic factor status.
***N1 includes N1mi. T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3 N1 and T4 N1, respectively.

Notes:

1. Because N1mi categorization requires evaluation of the entire node, and cannot be assigned on the basis of an FNA or core biopsy, N1mi can only be used with Clinical Prognostic Staging when clinical staging is based on a resected lymph node in the absence of resection of the primary cancer, such as the situation where sentinel node biopsy is performed prior to receipt of neoadjuvant chemotherapy or endocrine therapy.
2. For cases with lymph node involvement with no evidence of primary tumor (e.g. T0 N1, etc.) or with breast ductal carcinoma *in situ* (e.g. Tis N1, etc.), the grade, HER2, ER, and PR information from the tumor in the lymph node should be used for assigning stage group.
3. For cases where HER2 is determined to be "equivocal" by ISH (FISH or CISH) testing under the 2013 ASCO/CAP HER2 testing guidelines, the HER2 "negative" category should be used for staging in the Clinical Prognostic Stage Group table.[81,82]
4. The prognostic value of these Prognostic Stage Groups is based on populations of persons with breast cancer that have been offered and mostly treated with appropriate endocrine and/or systemic chemotherapy (including anti-HER2 therapy).