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Clinical Practice Guidelines - Breast Disease Site

Guideline Title:	Baseline Staging of Primary Breast Cancer - **Summary**	**Date:**	**(O):**	July 31, 2011
			(R):	June 30, 2022
Tumor Group:	Breast Disease Site Group	**Page:**		1 of 11
Issuing Authority:	Dr. Teri Stuckless Clinical Chief, Cancer Care Program	**Date Signed:**		Aug 31, 2023
Adapted From:	Cancer Care Ontario (CCO) “Baseline Staging Imaging for Distant Metastasis in women with stage I, II, and III Breast Cancer” guideline, October 2019 (5).			

Target Population:

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

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.

Supporting Evidence:

Early studies have indicated that conventional staging investigations reveal a low incidence of metastatic disease in asymptomatic patients diagnosed with early-stage breast cancer (1-3). 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. Research evidence at that time 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% (4). 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. The above systematic review also identified patients with IBC has having a median distant metastatic detection rate of 39.6% during baseline testing. Findings indicated that these patients were much more likely to have metastatic disease at presentation and warranted the use of baseline staging investigations.

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 (5). In comparison, patients diagnosed with stage III breast cancer, functional PET-CT imaging detected metastases in 26% of the cases. The consensus of the CCO working group indicates that there is no role for the use of PET-CT investigations in patients having stages I-II breast cancer and PET-CT is best used in situations where the findings of standard staging studies are equivocal or suspicious.

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) (7). 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. While many Canadian physicians are aware of, and agree with, existing guidelines on imaging for staging purposes, adherence to these guidelines is inconsistent. Across Canada, more work is necessary to eliminate unnecessary baseline staging investigations for patients with early-stage breast cancer.

Conflicting data exists has to whether the molecular biomarker status should influence the use of baseline staging investigations in breast cancer. The results of a systematic review suggested that the metastatic detection rate of baseline staging increased in accordance with stage of disease (i.e., tumor size and number of lymph nodes involved) (8).However, some recent individual studies have suggested that there may be certain subgroups, such as stage IIB with pathological lymph node involvement may also be at higher risk of recurrence and warrant the use of baseline staging investigations in order to detect metastatic disease earlier (9,10). 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. The Eastern Health Breast Disease Site Group believes in the

importance of implementing recommendations to help reduce the cost of over-using baseline staging investigations that do not provide meaningful benefit. However, 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. The Eastern Health BDSG has requested that surgeons order the required staging investigations (as outlined in Table 2) after pathological confirmation, and inform patients in order to expedite patients' journey through the healthcare system. However, family physicians, general practitioners, or nurse practitioners can also assume responsibility for ordering the necessary baseline staging investigations.

The Cancer Care Ontario guideline "Baseline Staging Imaging for Distant Metastasis in women with stage I, II, and III Breast Cancer" guideline was chosen by our working group to be adapted with modifications, for the development of this Eastern Health guideline.

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

Stage and Indication	Subtypes			
	Luminal A	**Luminal B**	**HER2+**	**Triple Negative**
Stage I and II • <T3 disease • No positive lymph node (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.*

Qualifying Statements:

1. 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" (6).

2. 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' (11). 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.

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:

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Literature Support:

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Appendix:

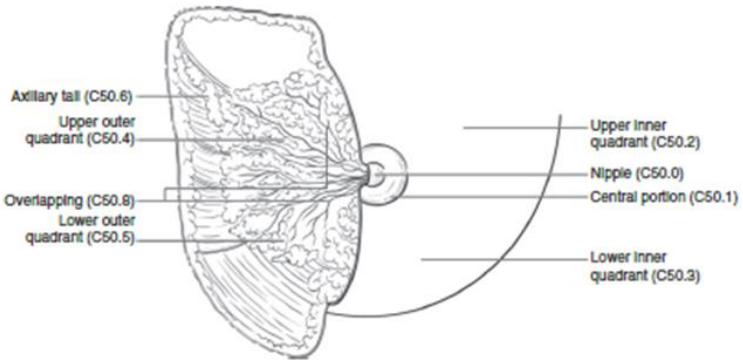

Fig. 48.1 Anatomic sites and subsites of the breast

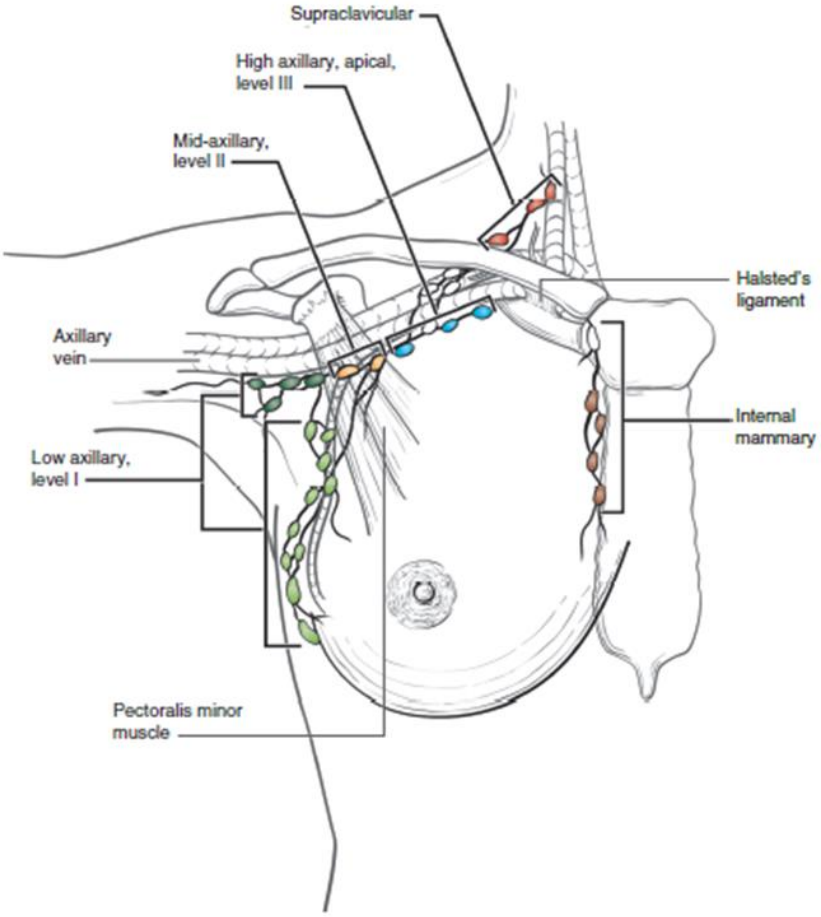

Fig. 48.2 Schematic diagram of the breast and regional lymph nodes

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).