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Clinical Practice Guidelines - Breast Disease Site

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Adapted From:	National Comprehensive Cancer Network (NCCN) “Breast Cancer” guideline, September 2019 (102).			

Introduction:

The primary management of breast cancer has seen considerable changes over the last decade. The use of neoadjuvant or preoperative treatment has evolved from its use in inoperable breast cancers, including the locally advanced or inflammatory cases, to its utilization for operable cancers as well. Breast conservation therapy (BCT), a combination of both breast conserving surgery (BCS) and radiation therapy (RT), which had once been used primarily for operable breast cancers, can now also be considered for some inoperable breast cancers. Neoadjuvant systemic therapy (NST) is the administration of pharmaceutical agents, prior to the definitive surgical procedure and potentially followed by radiation therapy as well as further systemic therapy such as endocrine or monoclonal antibody therapy, if eligible, and is a widely accepted method in the sequencing of cancer treatment. The pharmaceutical agents used include cytotoxic drugs, targeted therapies, and/or endocrine therapies which have been shown to potentially improve survival, local control, and operability. The increased use of the neoadjuvant treatment approach also has the potential to alter the surgical and/or radiation therapy plan for these patients. Multidisciplinary evaluation and planning are crucial in the use of NST to ultimately improve patient outcomes.

Questions:

1. What defines an inoperable versus an operable breast cancer and what are the goals of treatment for each?

2. How does breast cancer subtyping affect the choice of neoadjuvant treatment offered to patients with pathologically confirmed breast cancer?

3. What surgical and/or radiation therapy (RT) standard procedures have changed to reflect recent clinical research findings?

Target Population:

These recommendations apply to patients with a pathological confirmed diagnosis of invasive breast cancer.

Supporting Evidence:

A 2005 meta-analysis of studies, comparing neoadjuvant to adjuvant systemic therapy for the treatment of breast cancer, found that neoadjuvant therapy was equivalent to adjuvant therapy in terms of survival and overall disease progression (1). A more recent meta-analysis concluded that pathologic response to neoadjuvant chemotherapy was a prognostic indicator for relapse-free survival (RFS), disease-free survival (DFS), and overall survival (OS) and reported that patients achieving pathological complete response (pCR) after neoadjuvant chemotherapy had more favourable outcomes than those who did not (2). At present, the focus on neoadjuvant treatment has been to try to achieve higher rates of pCR by selecting multi-pharmaceutical regimens according to the patient's specific subtype of breast cancer.

*Pathological Complete Response (pCR)***:** In a pooled analysis of twelve international neoadjuvant breast cancer clinical trials, an investigation into which definition of pCR best correlated with superior long-term outcomes was carried out (3). This analysis looked at three definitions of pCR which included ypT0 ypN0 (absence of invasive cancer and insitu cancer in the breast and axillary nodes), ypT0/is ypN0 (absence of invasive cancer in the breast and axillary nodes, irrespective of ductal carcinoma in situ (DCIS)), and ypT0/is (absence of invasive cancer in the breast, irrespective of DCIS or nodal involvement). The investigators concluded that the ypT0 ypN0 definition was too restrictive and would likely reduce the number of pCR in the clinical setting. In addition, this study found that the presence of DCIS did not affect the long-term survival outcomes for these patients. In contrast, and as expected, the ypT0/is definition was not associated with positive long-term outcomes. Therefore, the Eastern Health Breast Disease Site Group (BDSG) recommends that the definition of a **pCR** is the absence of invasive cancer in the breast and axillary nodes, irrespective of DCIS (or **ypT0/is ypN0**).

Inoperable Breast Cancer

Historically, neoadjuvant systemic therapy (NST) was first used in an attempt to make large, locally advanced breast cancers amenable to surgical removal. Inoperable breast cancers are those presenting with either extensive local disease for which surgically negative margins are not a certainty, or those presenting with inflammatory breast cancer. The optimal management of inoperable breast cancers would be a combined-modality approach, with NST followed by locoregional therapy of surgery and radiation, and if eligible, followed by adjuvant endocrine therapy and possibly further anti-human epidermal growth factor receptor 2 neu (HER2) overexpression therapy. The advantages of NST treatment for these patients include:

- Earlier treatment of distant micrometastases;
- Downstaging of primary tumor;
- Potential for improved operability;
- Allows in vivo assessment of response to specific systematic agents (4).

Locally advanced breast cancer (LABC) is any primary tumor greater than 5 centimeters (cm) in diameter and/or that involves the skin or chest wall. It also includes patients with fixed axillary lymph nodes or ipsilateral supraclavicular, infraclavicular, or internal mammary nodal involvement. A national Canadian expert consensus group defined LABC as "...T3 or T4 tumors of any clinical N status, or any size tumor classified N2 or N3" (5). The latest Canadian Cancer statistics of the relative 5-year OS rate for LABC or stage 3 breast cancer is 72% (6). LABC is a heterogeneous disease which may include a range of all of the molecular subtypes and more likely to have substantial nodal involvement. Some patients with inoperable breast cancer can be candidates for BCS, if so desired, especially if a clinical complete response (cCR) has been achieved. However, many patients with LABC will still require a modified radical mastectomy (MRM) due to clinical situations where it remains the best option for long term control and improved outcomes, such as inflammatory breast cancer or in the presence of multicentric disease (more than two lesions in different quadrants). Patients with inoperable breast cancer are often candidates for locoregional radiation therapy (RT), and if BCS is an option, they should be presented at a multidisciplinary tumor board for discussion.

Inflammatory breast cancer (IBC) is a rare and aggressive form of breast cancer, defined clinically by the rapid development of erythema and edema (peau d'orange) of at least one third of the overlying skin of the breast, often without a palpable mass (7). Though often grouped under locally advanced breast cancer heading, IBC is a distinct biological disease from the more common ductal carcinoma seen in most LABCs. It can mimic mastitis (bacterial inflammation of the mammary gland) leading to delay in appropriate diagnosis and treatment. Despite improvements in the 5-year OS rates with the addition of anti-HER2 and hormonal therapies, IBC is still associated with a poorer prognosis than other LABCs. The latest American statistics from the National Cancer Institute Surveillance Epidemiology and End Results (SEER) reports that with treatment, the relative 5-year OS for patients with IBC is 39% (8).

Operable Breast Cancer

A Cochrane review of 14 eligible studies found pre-operative systemic treatment of women with an operable (or early) breast cancer to be a safe treatment option while improving the rate of BCT (9). *Operable breast cancer* has been defined as tumors not more than 5 cm in diameter, with either impalpable or palpable but not fixed, lymph nodes with no evidence of distant metastases (9). Patients who have operable breast cancer are those deemed most likely to be candidates for BCT. However, there are tumoral factors that may inhibit the use of immediate BCS such as a high tumor-to-breast ratio (i.e., those with small breasts/large tumors) or tumor location which can interfere with achieving a satifactory cosmetic outcome (106,108). Therefore, patients diagnosed with stages I to III breast cancer having either of these tumoral factors would be appropriate candidates for NST which has the potential to downstage tumors, following which BCS may become an option.

Certain breast cancer subtypes (triple negative (TN) or human epidermal growth factor receptor 2 overexpression (HER2+)) are known to be highly chemotherapy-sensitive and the introduction of NST increases the likelihood of a pCR which is associated with improved DFS and OS (3,10). Therefore, the Eastern Health BDSG recommends that patients with stage II or III operable breast cancer who have been confirmed to have TN or HER2-positive subtype on core biopsy, should be offered NST.

An international expert panel stated the goals of NST in operable breast cancer were:
- to acquire early information on response and biology of the disease;
- to improve surgical options;
- and improve DFS and OS outcomes (11,101).

The neoadjuvant GeparTrio Trial enrolled 2064 patients with IBC, LABC and operable breast cancer and found that tumor stage, itself, was not an independent predictor of pCR. Rather similar treatment response patterns were noted throughout all stages of breast cancer (12). Therefore, selection of neoadjuvant systemic therapy should be based on the molecular biomarker subtype (hormone receptor status and HER2 *neu* status) regardless of whether the tumor burden is operable or inoperable. Patients who undergo BCS will also require radiation therapy (RT) to the breast and/or axilla.

Assessment and Staging

All patients being considered for NST should undergo a full staging workup which includes:
- History and physical examination
- Diagnostic bilateral mammogram, and ultrasonography as directed
- Core needle biopsy of the breast and/or axillary tumor
- Pathological review of the tumor histology and biomarkers
- Complete blood count, as well as renal and liver function tests
- Pre-treatment breast magnetic resonance imaging (MRI) to aid in identifying tumor response to treatment, where feasible
- Computed tomography (CT) of chest and abdomen
- Bone scan
- Fluorodeoxyglucose positron emission tomography (FDG PET) is optional in those with inflammatory breast cancer or when the presence of distant metastases is in question
- Presentation at multidisciplinary Breast Tumor Rounds as necessary
- Fertility counseling where appropriate; and
- Genetic counseling if patient is at risk of hereditary breast cancer (101,102,104 -108).

Neoadjuvant Radiological Imaging of the Breast

Prior to the initiation of neoadjuvant treatment, the patient must undergo a full breast imaging profile, including bilateral diagnostic mammography with magnification and compression as needed, and ultrasonography. Magnetic resonance imaging (MRI) of the breast is the optimal imaging modality in assisting the clinician in determining whether the tumor has responded to NST (as per Eastern Health's "Indications for Use of Breast Magnetic Resonance Imaging (MRI)" guideline) (13). This recommendation has been supported by the Response Evaluation Criteria In Solid Tumors (RECIST) and based upon expert opinion and recommendations of several current national and international guidelines (14,101,103,106,108). A baseline breast MRI is strongly recommended prior to the commencement of NST and again, mid-treatment for comparative purposes. The pre-treatment breast MRI is best ordered by the surgeon, shortly after the initial assessment to expedite the imaging and prevent unnecessary delays for patients who will benefit most from NST. In addition to imaging, clinical assessment of the breast is essential during treatment to allow for monitoring of tumor response, especially in the case when clinical response is unclear. The clinical usefulness of breast MRI for the purposes of surgical/radiation planning has been a topic of debate due to the breast MRI's wide range of specificity, making its

utilization an individual choice among surgeons rather than a recommendation (15). However, breast MRI imaging does have some additional diagnostic value when evaluating situations which include the presence of multifocal or multicentric disease, screening for malignancy in the contralateral breast, occult breast lesions with axillary metastases only, and detection of lesions in dense breasts (15,16). During the imaging procedures, core needle biopsies of all suspicious lesions should be performed. In comparison to a fine needle aspiration (FNA), the core needle biopsy has been found to be the best diagnostic method for detection of malignant breast lesions and allows for more detailed biomarker testing which provides information on the nature of the tumor, itself (17). An ultrasound of the axillary lymph nodes should also be carried out to assist in staging the axilla and FNA or core biopsy of any suspicious findings should be carried out.

Breast imaging (mammogram, spot compression views, ultrasound) of the local/regional tumor burden is essential, not only to provide information on in-vivo tumor response to NST, but also for the surgical/radiation therapy planning components, especially if BCT is desired. Neoadjuvant chemotherapy has the potential to completely eradicate breast tumor(s), therefore the Canadian Association of Radiologists recommends that radiopaque tissue markers or clips should be inserted under radiographic imaging to accurately identify the initial tumor bed (16,18). An M. D. Anderson Cancer Center retrospective review has often been reported as evidence to support the use of these radiopaque markers (19). In this study, 410 nonmetastatic breast cancer patients who had undergone anthracycline-based chemotherapy and BCT, found that the placement of radiopaque clips in this population was associated with better local control independent of stage and other clinicopathologic findings. There are no existing standards to dictate the number or location of these radiopaque marker(s), clip(s), or, in some cases, a coil(s) used but in general, only one is inserted into the center of the tumor. However, one or more may be inserted into the periphery of the tumor upon request by the surgeon. When patients are diagnosed with multifocal breast cancer, clip placement is recommended in the primary tumor as well as any satellite lesions (19,101-108). However, currently no imaging modality has been validated to predict the safety of performing BCS over mastectomy for every patient.

A recent systematic review found that FDG PET detected additional locoregional lymph node metastases and distant disease in approximately 10% of patients versus that of conventional imaging, as well as better diagnostic performance (20). Therefore, FDG PET has been recommended has a staging option for those diagnosed with inflammatory breast cancer.

Pathology Review

Breast cancer is a heterogeneous disease and the probability of survival appears to depend more on the combination of tumor biomarkers than their individual contribution. Gene expression profiling studies of breast tumors have identified at least four categories: luminal A, luminal B, human epidermal growth factor receptor 2 (HER2 *neu*) overexpression, and triple negative/basal-like, as per Table 1 (21,22). The process of determining the breast cancer molecular subtype from the core biopsy tissue sample is crucial in developing the most appropriate management regimen for the patient. For information regarding breast cancer staging, please see the 8th edition of the American Joint Committee on Cancer staging manual in the appendix (112).

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

An adjuvant Dana-Farber Cancer Institute study, in which patients did not receive trastuzumab (or a biosimilar agent) or other anti-monoclonal therapy for those subgroups with HER2 *neu* overexpression, showed that the 5-year cumulative incidence of distant metastases by subgroup was 3.3% for the luminal A, 12% for the luminal B, 19% for the HER2 *neu* overexpression type, and 16% for the triple negative (TN) (21). The women with luminal A subtype breast cancer having strongly positive estrogen and progesterone positivity, were found to have the best 5-year relative cumulative survival rate, while all estrogen receptor (ER)-negative subtypes were worse. In all HER2 *neu* overexpressing tumors, women with the ER negative/progesterone receptor (PR)-negative/HER2 *neu* positive (HER2+) subtype, who had not received adjuvant trastuzumab had the worst survival, comparable to the TN subtype. These two subtypes are also significantly more likely to be grade 3 (ie. have poorly differentiated tumors) when compared to luminal A tumors (21,22). However, there is now ample evidence to suggest that the addition of 1 year of anti-HER2 therapy, such as trastuzumab, to the adjuvant chemotherapy regimen for the treatment of HER2+-breast cancer improves both DFS and OS in these patients. These results aided in determining that adjuvant trastuzumab would become the standard of care for treating patients having HER2 *neu* positive disease. Long term data from two large analyses of patients with HER2-positive early breast cancer indicate that the addition of trastuzumab has an estimated OS benefit at 5 years of 91% to 92% and a 10-year OS rate of 75.2% to 84% (23,24). In addition, the DFS at 5 years was 81% to 84% and 62.2% to 73.7% at 10 years. As a result, TN breast cancers are now considered to have the poorest prognosis and the highest likelihood of relapse of all breast cancer subtypes.

Molecular Biomarker Subtypes

Luminal A breast cancers, with its characteristics of high expression of ER, low proliferation or low grade, and no amplification or overexpression of HER2 *neu* oncogene, are believed to receive little or no added benefit from chemotherapy, when compared to endocrine therapy alone (25,26). Neoadjuvant endocrine therapy (NET) has often been used to treat locally advanced, hormone receptor (HR) positive breast cancer in the elderly and patients for whom chemotherapy is contraindicated, or for those with a more favorable pathology (i.e., non-pleomorphic lobular carcinoma, tubular, or low-grade mucinous tumors). However, the results of a recent clinical trial revealed that even premenopausal women with high-risk Luminal A breast cancer do not derive any benefit from cyclophosphamide-based chemotherapy (27). Therefore, even this subgroup of patients with Luminal A disease are appropriate candidates for NET.

Luminal B breast cancers are a much more heterogeneous group then those within the luminal A subtype. The luminal B subtype tends to have a lower expression of ER-regulated genes with or without overexpression of HER2 *neu*, accompanied by a higher expression of proliferative genes, which accounts for its poorer long-term outcomes (28,29). Ki67 is a nuclear marker of cell

proliferation where higher levels are associated with worse outcomes in these breast cancers (30). Ki67 is being used in some centers as a clinically valuable biomarker for the luminal B subtype. However, there is inconsistency in cutoff values used in studies which has created a lack of standardization of Ki67 measurements. Therefore, at present, it is not a routinely utilized test in clinical decision-making (30,31).

The HER2 *neu* subtype has an overexpression of HER2 *neu* related genes and is reported to make up 15-20% of all breast cancers, with approximately 50% of which having a low to negative expression of ER-related genes (32). In general, ER negative tumors are associated with higher pCR compared to ER positive tumors after neoadjuvant chemotherapy (33-36). One study's findings suggested that HR-/HER2+ breast cancers had a two-fold pCR response rate (29%) compared to HR+/HER2+ breast cancers (15%) after NST with anti-HER2 therapy ($p< 0.001$) (37). Prior to the introduction of anti-HER2 therapies such as trastuzumab (or a biosimilar agent), the prognosis for women having HER2+ disease was poor with few pCRs. A planned joint analysis of two clinical trials, NSABP B-31 and NCCTG N9831, explored the OS results when trastuzumab was added to adjuvant chemotherapy in HER2+ breast cancer (38). The results of this joint analysis found that the addition of trastuzumab provided a 40% improvement in DFS and a 37% relative improvement in OS and an increase in the 10-year DFS and OS rates.

The triple negative (TN) or basal-like subtype has low expression of ER-related and HER2-related genes, and therefore is resistant to some of the most effective therapies (i.e., trastuzumab, selective estrogen receptor modulators (SERMs), aromatase inhibitors) available for breast cancer (39). TN breast cancers account for 15-20% of all breast cancers and are characterized by rapid growth with a high recurrence rate and short interval between recurrence and death (40). Most breast cancers with a BRCA1 mutation have a TN/basal-like phenotype (39,41). However, many TN breast cancers are extremely sensitive to chemotherapy and tend to have higher rates of pCR (approximately 30% post-NST) then luminal subtypes (40).

Molecular Subtype Cutoffs

ER/PR**:** In 2010, the American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) recommended that ER and PR assays be considered positive if there are at least 1% positive tumor nuclei in the sample on testing in the presence of expected reactivity of internal (normal epithelial elements) and external controls (42). This came as a result of the conclusion that up to 20% of current immunohistochemistry (IHC) determinations of ER and PR testing worldwide may be inaccurate (false negative or false positive), with most of the issues with testing occurring because of variations in pre-analytic variables, thresholds for positivity, and interpretation criteria.

However, in the 2018 German Gynecological Oncology Group (AGO) guideline noted that these 2010 ASCO/CAP recommendations mentioned above were developed during a time when IHC testing was much less sensitive than it is presently (104). Recently, research has suggested that tumors having low ER staining of 1% to 10% share several features of TNBCs such as BRCA status, gene expression profiles, and prognosis (43-45). Therefore, the German AGO group recommended that these tumors be defined as *"low positive"* though the clinical consequences of this differentiation remain unclear. A retrospective study out of the MD Anderson Cancer Centre, evaluated outcome and response to hormone treatment in 9639 patients with ER staining of ≥10%, 1% - 9%, and <1% (45). This study reinforced previous findings which suggested that

clinicopathological characteristics again did not differ significantly between the tumors with 1% - 9% and <1% ER staining groups. These two groups tended to be younger with more advanced disease and poorer survival in comparison to the ≥10% ER staining group. The ASCO/CAP guideline developers published their update in January 2020 which aligned with the definition for >1% to <10% ER expression as ER Low Positive (46).

In conjunction with the new ASCO/CAP guideline update, the consensus of the Eastern Health Breast Disease Site Group (BDSG) is that patients who have tumors with less than 10% ER expression are highly unlikely to respond clinically to neoadjuvant endocrine therapy (NET). Therefore, after careful consideration, the Eastern Health Breast Disease Site Group will not offer NET to patients whose tumors have less than 10% ER expression. Exceptions may be made for patients where pre-existing co-morbidities or advanced age exist which may preclude the use of chemotherapy and would be used mainly as a palliative measure.

For the purposes of this guideline, the following measurement criteria will be used to help determine the optimal chemotherapy regimen:

Luminal A**:** A subgroup of “highly endocrine-sensitive” tumors, (as described by the St. Gallen expert group, 2007) that have both ER and PR expression in more than 50% of the nuclei on IHC assays and lack HER2 *neu* amplification (47).

Luminal B (Ki67)**:** In 2011, the “International Ki67 in Breast Cancer Working Group” stated that Ki67 measurement by IHC is the current assay of choice for measuring and monitoring tumor proliferation in standard pathology specimens (48). However, this group did recognize the inter-laboratory variability of validity in methods of assessment. Currently, Ki67 test scoring has still not been standardized or validated for breast cancer tumor assessment. The St. Gallen international expert consensus of 2011, noted that if reliable Ki-67 labeling index assessment is not available, some alternative measure of proliferation such as histological grade may be used in making the distinction between luminal A and luminal B (HER2 *neu*-) subtypes (27).

HER2 *neu***:** Previously, two technologies were recognized for use in the determination of HER2-amplification in breast cancer. Strong IHC staining (3+) of >30% of the tumor cells would represent an overexpression of the HER2 protein, while 1+ result was indicative of no overexpression and therefore considered negative. An equivocal result of 2+ would be further evaluated by fluorescence in situ hybridization (FISH): ratio of HER2 *neu* gene copies to chromosome 17 centromers > 2.2) or by chromogenic in situ hybridization (CISH): more than 6 HER2 signals per cell) to determine if gene amplification were present (47,49).

For the purposes of this guideline, the molecular categories and biomarker subtypes as well as the Eastern Health BDSG's recommended cutoffs are listed in Table 2.

TABLE 2: **Four Molecular Breast Cancer Subtypes and Cutoffs**

Subtype	Molecular Markers and Cutoffs
Luminal A	Estrogen receptor (ER) positive and progesterone receptor (PR) strongly positive (both ER and PR expression ≥ 50%), HER2 negative, low Ki67 (or low grade tumors)
Luminal B	ER positive and/or PR positive (either ER or PR ≥ 10%), HER2 positive or HER2 negative with high grade tumors
HER2 neu positive	ER negative and PR negative (< 1%) or ER and PR low (1% - 9%), HER2 positive
Triple Negative/Basal-like	ER negative and PR negative (< 1%) or ER and PR low (1% - 9%, HER2 negative

Molecular Biomarker Testing

The Eastern Health BDSG recommends that all core biopsy(s) of confirmed invasive breast cancer should have molecular biomarker testing performed to help identify patients who could benefit from NST, in particular those with TN or HER2-positive subtypes. As a diagnostic method, the core needle biopsy is well established and known to be effective and reliable in providing histopathological confirmation of breast carcinoma (50-52). Unlike a fine needle aspirate, a core biopsy provides sufficient tissue to allow for the immunohistochemical assessment of molecular biomarkers consistently. Testing molecular biomarkers on core biopsy(s) has become standard of care for those who may be eligible for NST and as demonstrated by all eight national and international guidelines referenced in this document (102 -109).

Re-testing for Molecular Biomarker Subtype on Definitive Surgical Specimen

The Eastern Health BDSG also recommends that all biomarker subtypes, other than those who tested triple positive (ER-positive/PR-positive/HER2-positive) on the core biopsy, should have biomarker re-testing performed on any residual tumor(s) from the definitive surgical resection. Recent clinical trial data has highlighted discordance of the receptor status (and subsequent biomarker subtype) of invasive breast cancers between the core needle biopsy and that of the residual specimen removed during the definitive surgical procedure, especially when NST has been administered (53,54). A UK clinical trial studied the biomarker test results of the core needle biopsy and surgical specimen in 246 cases of operable breast cancer who received NST and 113 of a paired core biopsy and surgical specimen, control group (no NST) (55). The findings indicated that significant changes occurred in the biomarker test results between the core biopsy and surgical specimen which affected the molecular type classification status of the cohort who received NST. The changes in ER/PR/HER2 status occurred respectively, in 12%, 14.5% and 7.1% ($p < 0.001$) of the cases. Most of the ER cases switched from negative to positive while more of the HER2 cases switched from positive to negative. The oncologists in the BDSG have agreed that they, as well, have noticed a similar pattern of discordance in breast cancer patients in this province between the core biopsy and definitive specimen biomarker results. The greatest concern regarding the discordance is the potential for the dramatic implications it can have for treatment choice and potential survival of this patient cohort

Breast cancer is known to have both *intertumor* (differences among patients) and *intratumor* (differences within an individual tumor) heterogeneity (56). Re-testing the biomarkers on the definitive surgical specimen provides an opportunity to find pathological intratumor heterogeneity. When intratumor heterogeneity exists within a patients tumor, the potential is that different molecular subtypes can be found in various locations of the same tumor. This allows the medical oncologist the option of introducing systemic therapy (e.g. endocrine therapy, anti-HER2 treatment), suitable for those who convert to a positive receptor status. This new treatment introduction can still occur in the adjuvant setting while cure is still the goal. Therefore, if a patient's tumor had triple positive biomarkers (ER-positive, PR-positive, HER2-positive) on core biopsy, this is the only situation where biomarkers need NOT be repeated on the definitive surgical specimen.

The practice of retesting biomarkers on definitive surgical specimens after NST has also been supported by some well-respected national and international cancer guideline development organizations. These include the Canadian Consortium for locally advanced breast cancer, as well as international groups such as the American group National Comprehensive Cancer Network (NCCN), and two European groups, the European Society for Medical Oncology (ESMO), as well as, the European Group on Tumor Markers (EGTM) (57,102,104,107). This practice was also supported by the latest update of the ASCO/CAP "human epidermal growth factor receptor 2 testing in breast cancer" guideline (58).The guideline update for ASCO/CAP "estrogen and progesterone receptor testing in breast cancer" does not recommend retesting for ER/PR receptors. However, the authors have been criticized for not considering the clinical implications of intratumor heterogeneity (59).

Neoadjuvant Systemic Therapy (NST)

In clinical practice, the standard neoadjuvant approach is to treat the patient with the same chemotherapy regimens that would be offered in the adjuvant setting. All chemotherapy provided neoadjuvantly should be given prior to surgery rather than divided into preoperative and postoperative phases (60). Anthracyclines had formed the basis of standard neoadjuvant chemotherapy, but research has shown that the addition of the taxanes, docetaxel or paclitaxel, to anthracyclines resulted in improved response for most cancer subtypes (61 – 63).

The introduction of trastuzumab, a recombinant humanized monoclonal antibody which targets HER2 *neu*, in combination with chemotherapy, has revolutionalized the treatment of HER2 *neu*-positive breast cancers in the metastatic/adjuvant setting. Neoadjuvant use of trastuzumab and chemotherapy has also been found to significantly increase the pCR rate and provides improvement in disease-free, overall, and event-free survival compared to neoadjuvant chemotherapy alone (64 – 68). The GeparQuattro study, of over 1500 patients with operable and locally advanced breast cancer, were treated with four cycles of epirubicin/cyclophosphamide followed by four cycles of docetaxel, with or without capecitabine, as well as trastuzumab for those with HER2 *neu*-positive tumors, every 3 weeks (69). The HER2 *neu*-positive cohort was compared to the HER2 *neu*-negative one which revealed a pCR of 31.7% and 15.7%, respectively. Biosimilars of trastuzumab are now available and have been approved for use in Canada.

A phase II neoadjuvant NeoSphere trial studied the addition of a second HER2 *neu*-directed therapy, pertuzumab, to the standard treatment of trastuzumab plus chemotherapy for patients with locally advanced, inflammatory, or early-stage HER2 *neu*-positive breast cancer (70). The

four arms of the study included A: trastuzumab and docetaxol; B: pertuzumab, trastuzumab and docetaxol; C: pertuzumab and trastuzumab; D: pertuzumab and docetaxel. The primary endpoint of this study was pCR. The results suggested that arm B had a significantly improved pCR rate of 45.8% (95% CI: 36.1 - 55.7) compared to arms A, C, and D (29% vs 16.8% vs 24%), respectively. Recently the 5-year analysis published results suggested that the use of a dual HER2 *neu* blockade, with standard docetaxel chemotherapy (arm B), improved progression-free survival (PFS)(analyzed in the intent-to-treat population) and DFS (analysed in patients who had surgery) compared to the other three arms (71). The authors concluded that the large and overlapping confidence intervals of PFS and DFS supported the primary endpoint of pCR which suggests a benefit of including pertuzumab to standard treatment of trastuzumab and docetaxel. The findings of this study were also supported by similar findings in the neoadjuvant cardiac safety TRYPHAENA trial suggesting that the addition of dual HER2 *neu* blockade improved the pCR rates, PFS, and DFS (72). In addition, the safety profiles of both of these studies, as well as that of the CLEOPATRA trial, using pertuzumab, trastuzumab and standard chemotherapy in the metastatic setting, indicated that the combination of two HER2 *neu*-directed therapies were similar to those of a single HER2 *neu*-directed therapy, with no worsening of expected side effects (73). The use of dual HER2 *neu* agents in addition to docetaxel chemotherapy has proven to be efficacious and is highly recommended for those patients at high risk of recurrence in the latest national and international guidelines (102,103,105 – 108). At present, pertuzumab is unavailable in Canada for this indication however it may be pending future approval from the pan-Canadian Pharmaceutical Alliance (pCPA).

Presently, there is no role for the use of anti-angiogenic targeted agents, such as bevacizumab, in the neoadjuvant treatment of breast cancer.

Inflammatory Breast Cancer and NST

Research has revealed that inflammatory breast cancers tend to have a higher incidence of both negative ER and PR status and an overexpression of HER2 *neu* than non-inflammatory breast cancers (74,75). Multimodality treatment with combination neoadjuvant chemotherapy has improved outcomes, which an international expert panel on inflammatory breast cancer recommends should include an anthracycline and a taxane, followed by surgery and radiation (76). For those whose biomarker testing are found to be HER2 *neu*-positive, trastuzumab should be included in the treatment regimen, but historically has not been given concomitantly with anthracyclines, due to a previously established, increased risk of cardiac toxicity. However, debate has arisen as to the accuracy of this statement and the safety of giving concurrent anthracyclines and trastuzumab is being investigated. Currently, a nonanthracycline regimen can be considered such as a taxane, carboplatin and trastuzumab, followed by surgery, then radiation, one year total of trastuzumab treatment, and adjuvant endocrine therapy if indicated. A MRM followed by locoregional RT is standard of care. BCS is not an option for patients with inflammatory breast cancer.

Neoadjuvant Endocrine Therapy (NET)

Research has shown that ER-positive breast cancer tumors are less sensitive to chemotherapy than those which are ER-negative, and the benefit of chemotherapy is believed to decrease with age (77). Tamoxifen has efficacy as a NET agent in the treatment of locally advanced tumors and operable breast cancers, especially in the elderly. Though, a growing body of evidence suggests that for ER-positive postmenopausal patients, aromatase inhibitors are more effective than

tamoxifen in providing a better objective clinical and radiological response, and higher breast conservation rates (78-81). One Japanese phase III study enrolled premenopausal patients, who received goserelin monthly, and were randomized to receive either anastrozole or tamoxifen for a 24-week neoadjuvant treatment period. It found that more patients in the anastrozole group had a complete or partial response than those in the tamoxifen arm (70.4% vs 50.5%;p = 0.004) (82).

There are few clinical trials which have done a head-to-head comparison of NET to neoadjuvant chemotherapy. However, one phase II trial looked at the efficacy of endocrine agents (either anastrozole or exemestane) versus chemotherapy (doxorubicin/paclitaxel) used in the neoadjuvant setting for the treatment of ER-positive breast cancer, irregardless of HER2 *neu* status, and who were ineligible for BCS from the onset (83). It found at 3 months no statistically significant difference in overall objective response between the two groups. Although more patients were eligible for BCS in the endocrine group than the chemotherapy group (33% vs 24%; p = 0.058), this was not statistically significant. After a median followup of 36 months, no significant difference was found in the incidence of local recurrence between the two groups.

An international consensus conference on neoadjuvant systemic therapy for breast cancer recommends the option of NET, with aromatase inhibitors, for at least 4 months and possibly up to 8 months for postmenopausal patients with ER-positive breast cancer (60,84). However the results of several clinical trials found that extending the administration of aromatase inhibitors in the neoadjuvant setting was superior in achieving maximum reduction in tumor volume (85-89). Therefore, the Eastern Health BDSG recommends that the treatment course for NET with aromatase inhibitors will be extended from at least 6 months and possibly as long as 12 months for this patient cohort, dependent upon tumor response.

Pathological Complete Response (pCR) and Molecular Subtype
Historically, only 20-30% of patients have been able to achieve a pCR to NST, with the biology of certain tumors having an increased likelihood of doing so (90). In a German Breast/AGO meta-analysis, the working group reviewed the incidence and prognostic impact of pCR among breast cancer subtypes (10). The findings suggest that pCR is not prognostic for slowly proliferating tumors such as Luminal A and Luminal B/HER2 *neu*-positive subtypes (irrespective of trastuzumab treatment), but highly prognostic for HER2 *neu*-positive (nonluminal), TN and Luminal B/HER2 *neu*-negative tumors (40). Even when pCR rates are low within the Luminal A subtype treated with NET, this molecular subtype is frequently associated with a good prognosis regardless. Hence, it was determined from the literature that pCR is not a useful prognostic indicator in the Luminal A and some Luminal B/HER2-positive subgroups. The pooled CTNeoBC analysis found that the TN and HER2-positive phenotypes had the highest probability of achieving a pCR (TN was 33.6% and HER2-positive was up to 50.3%) after NST (3).

TABLE 2: **Neoadjuvant Systemic Therapy Regimens According to Molecular Breast Cancer Subtypes**

Molecular Subtype	Neoadjuvant Systemic Therapy Regimens
Luminal A	Neoadjuvant endocrine therapy (NET) options: • SERM such as tamoxifen OR aromatase inhibitor such as anastrozole, letrozole, or exemestane plus goserelin for premenopausal patients for 6 to 12 months; • aromatase inhibitor such as anastrozole, letrozole, or exemestane for postmenopausal patients for 6 to 12 months; OR Neoadjuvant chemotherapy options, including but not limited to: • taxane such as docetaxel or paclitaxel, and an alkylating agent such as cyclophosphamide (followed by endocrine therapy after definitive surgery);* • anthracycline and alkylating agent (followed by endocrine therapy after definitive surgery);* • alkylating agent, an antimetabolite such as methotrexate, and antimetabolite fluoropyrimidine such as 5-fluorouracil (followed by endocrine therapy after definitive surgery).
Luminal B	ER positive and/or PR positive, HER2 *neu*-positive (neoadjuvant chemotherapy options): • taxane, a platinum such as carboplatin, and trastuzumab or a biosimilar (trastuzumab, or a biosimilar agent, will continue alone once chemotherapy is completed for a duration of 1 year) (followed by endocrine therapy after definitive surgery);* • taxane, an alkylating agent, and trastuzumab or a biosimilar (trastuzumab or a biosimilar agent will continue alone once chemotherapy is completed for a duration of 1 year) (followed by endocrine therapy after definitive surgery);* • antimetabolite fluoropyrimidine, an anthracycline and an alkylating agent followed by a taxane and trastuzumab or a biosimilar (trastuzumab, or a biosimilar agent, will continue alone once chemotherapy is completed for a duration of 1 year) (followed by endocrine therapy after definitive surgery);* • or other anthracycline- and taxane-based chemotherapy regimen ≥ 6 cycles plus trastuzumab or a biosimilar (trastuzumab, por a biosimilar agent, will continue alone once chemotherapy is completed for a duration of 1 year) (followed by endocrine therapy after definitive surgery).* ER positive and/or PR positive, HER2 *neu*-negative (neoadjuvant chemotherapy options):

	• taxane, an anthracycline, and an alkylating agent (followed by endocrine therapy after definitive surgery);* • dose dense anthracycline and an alkylating agent, followed by a taxane (followed by endocrine therapy after definitive surgery);* • antimetabolite fluoropyrimidine, an anthracycline and an alkylating agent, followed by a taxane (followed by endocrine therapy after definitive surgery);* • taxane and an alkylating agent (followed by endocrine therapy after definitive surgery);* • or other anthracycline- and taxane-based chemotherapy regimen ≥ 6 cycles (followed by endocrine therapy after definitive surgery).*
HER2 neu positive	ER negative, PR negative, HER2 *neu*-positive (neoadjuvant chemotherapy options): • taxane and trastuzumab or a biosimilar (trastuzumab, or a biosimilar agent, will continue alone once chemotherapy is completed for a duration of 1 year), and potentially the addition of pertuzumab (upon approval);* • antimetabolite fluoropyrimidine, an anthracycline and an alkylating agent, followed by a taxane and trastuzumab or a biosimilar (trastuzumab, or a biosimilar agent, will continue alone once chemotherapy is completed for a duration of 1 year);* • dose dense anthracycline and alkylating agent, followed by a taxane and trastuzumab or a biosimilar (trastuzumab, or a biosimilar agent, will continue alone once chemotherapy is completed for a duration of 1 year);* • or other anthracycline- and taxane-based chemotherapy regimen ≥ 6 cycles plus trastuzumab or a biosimilar (trastuzumab, or a biosimilar agent, will continue alone once chemotherapy is completed for a duration of 1 year).*
Triple Negative, Basal-like	ER negative, PR negative, HER2 *neu*-negative (neoadjuvant chemotherapy options): • taxane, an anthracycline and an alkylating agent;* • antimetabolite fluoropyrimidine, an anthracycline and an alkylating agent, followed by a taxane;* • dose dense anthracycline and alkylating agent, followed by a taxane;* • taxane and an alkylating agent;* • or other anthracycline- and taxane-based chemotherapy regimen ≥ 6 cycles.* Residual Disease following neoadjuvant chemotherapy: • antimetabolite such as capecitabine.

**All neoadjuvant chemotherapy regimens containing anthracyclines and/or taxanes require prophlactic GCSF support as per the Eastern Health clinical practice guideline "Therapeutic Use of Myeloid Growth Factors for Chemotherapy-Induced Neutropenia in High Risk and Intermediate Risk Patients".*

Neoadjuvant Clinical Assessment
Frequent and accurate assessment of the breast, before and during treatment, is crucial for monitoring tumor response and potentially reducing patient morbidity. A thorough initial physical examination, including an assessment of the breast and axillary region as well as tumor measurement, should be performed prior to commencement of neoadjuvant treatment. Clinical assessment of the breast, with tumor measurement, should be carried out prior to each cycle of chemotherapy (usually every 2 - 3 weeks) or endocrine therapy (usually every 4 weeks). Ideally, this should be performed by the same physician to promote consistency in the assessment of treatment response. If the tumor fails to respond or progresses after 2 – 3 cycles of treatment, the medical oncologist must be notified to determine the next course of action. If the treatment response is questionable, MRI may be helpful (but only if a pre-neoadjuvant therapy MRI had been performed).

Poor Tumor Response and Residual Disease
Despite the use of effective neoadjuvant systemic therapies, most patients will either have only a partial response or no response at all which translates into higher recurrence rates and inferior outcomes compared to those who achieve a pCR (with the exception of luminal A and a subset of luminal B subtypes) (3). Historically, those patients who had a poor initial response to NST would often receive treatment modification which frequently did not result in any clinically meaningful improvement in outcomes (91,92). For those patients with operable disease, who have little or no response to NST, the decision may be to either proceed on to surgical intervention, or in some cases to attempt another different chemotherapy regimen(s).

In cases where the patients' disease is inoperable and initial NST results in poor tumor response (either no tumor shrinkage or increased tumor growth) as determined by clinical or radiological findings, presentation at a multi-disciplinary disease site group is the best option. In conclusion, the choice of medical management includes either:

- to attempt another different chemotherapy or endocrine therapy regimen(s);
- collaborate with a radiation oncologist to determine whether neoadjuvant locoregional RT is an option; or
- palliative RT for symptom control.

The goal of neoadjuvant therapy is to achieve pCR which is associated with improved DFS and OS. However, not all patients with breast cancer achieve it. Despite the higher rates of TN and HER2-positive subtypes achieving pCR compared to Luminal subtypes, approximately half of these patients (with TN and HER2-positive breast cancer) will have residual disease remaining in the affected breast at the end of the prescribed NST regimen. These patients found to have residual disease at the time of surgery are known to have a higher risk of recurrence and a poorer prognosis, than those who achieved a pCR (10). Residual cancer burden has been defined as the combination of pathologic measurements of size and cellularity of primary tumor, as well as, the number and size of nodal metastases providing a standardized procedure for the prospective evaluation of specimens in reporting response to neoadjuvant chemotherapy (89).

Recent clinical trials have shown some promise of improving outcomes for those who do not achieve pCR with standard neoadjuvant treatment regimens. The KATHERINE clinical trial looked at using trastuzumab emtansine (T-DM1), an antibody-drug conjugate of trastuzumab and cytotoxic agent, for patients who had residual invasive breast cancer in the breast or axilla at

surgery, after receiving NAC plus HER2 *neu*-targeted therapy (93). The primary endpoint was invasive DFS based on the intention-to-treat population. The interim analysis results indicated that invasive disease occurred in 22.2% of patients who received trastuzumab while only 12.2% of patients who received T-DM1 developed invasive disease. The authors concluded that those patients, with residual disease post-surgery, and treated with T-DM1 experienced a 50% risk reduction of breast cancer recurrence than those treated with trastuzumab alone. T-DM1 has only been approved in Canada for palliative treatment in the metastatic breast cancer setting however future approval for use in the neoadjuvant setting for those with residual disease is pending.

For those breast cancer patients with HER2-negative subtype, only 13% to 22% achieve a pCR after receiving NST (94). The CREATE-X study randomized patients with HER2-negative breast cancer (including TN and Luminal B subtypes), who had residual invasive BC at the time of surgery post-NST, to receive standard post-surgical care (control arm), or 6 – 8 cycles of adjuvant capecitabine chemotherapy (intervention arm). Both DFS and OS were found to be statistically higher in the intervention arm compared to the control arm, with the TN subgroup having the largest benefit in terms of both DFS and OS (94).

Surgical Oncology/Oncoplastic Surgery

The increasing prevalence for the use of a neoadjuvant approach has co-incided with the primary choice of surgeons to perform breast conserving and/or oncoplastic surgerical procedures on patients having either operable or initially inoperable breast cancer. Significant advances have been made in the role of oncological surgical procedures in the neoadjuvant setting in an attempt to reduce the negative side effects, such as mastectomy and/or lymphedema, while maintaining the clinical benefit for patients. Advances such as an accepted standardized approach to surgical margins of the breast and the increased use of SLNB have been highly effective in promoting breast conserving surgery resulting in better psychological outcomes,less disfigurement and improving cosmesis for women with invasive breast cancer.

Breast

Most of the national and international guideline organizations have embraced the use of Society of Surgical Oncology (SSO)/American Society for Radiation Oncology (ASTRO) definition of “no ink on tumor(s)” as the optimal negative marginal status in the surgical resection of breast cancer, provided all radiographic suspicious lesions have been resected (95). This standardized approach not only minimizes the risk for developing ipsilateral breast recurrence but can prevent unnecessary re-excisional surgeries or even mastectomy. All of the recent neoadjuvant breast cancer treatment guidelines tend to have a focus on BCS for both operable and initially inoperable invasive breast cancers. Therefore, if the patient obtains a clinical complete response (cCR) or partial response to NST in the breast which allows for complete removal of the tumor(s) while healthy tissue is retained, then a lumpectomy should be performed followed by RT to the remaining breast tissue. However, there are some clinical situations where mastectomy may still be the best option including inflammatory breast cancer, multicentric disease, large tumor-to-breast size ratio after NST, potential for poor cosmesis, and where there are contraindications to RT (109). The type of medical treatment to be offered must also consider the patients’ wishes, with final decisions reached via a consultation between the patient and surgeon.

Sentinel Lymph Node Biopsy (SLNB)
In recent years, SLNB has become standard of care for patients with invasive breast cancer who presented with clinically- or biopsy-negative axillary nodes, and remained so after NST (60,96). There has been significant debate regarding those patients presenting with biopsy-proven positive axillary lymph node(s) (cN1) who convert to negative after NST (ycN0). Though an axillary lymph node dissection (ALND) would appear to be overtreatment in this case, the concern most frequently expressed is the fear of false-negative results and potential for undertreatment using SLNB. NCCN suggests that SLNB can be used in select cases while St Gallen's guidelines recommends SLNB is sufficient if at least 3 or more sentinel nodes were identified and all were negative (102,104). Conversely, AGO suggests using targeted axillary dissection which involves the attachment of a radiological clip to the core needle biopsy-positive target lymph node(s) during pre-treatment assessment (103). Once NST as been completed, the sentinel node and the targeted node should be removed at the time of definitive surgery. This technique substantially reduces the false-negative rate (97,98). The Eastern Health BDSG agrees that the surgeon may avail of either of these techniques for patients deemed appropriate for SLNB, who convert to negative lymph nodes following NST. The results of several ongoing studies (RISAS, SENTA, GANEA 3) should be helpful in increasing the knowledge of whether SLNB is appropriate and safe to perform in this clinical situation. Patients who present with biopsy-proven positive axillary lymph node(s) of ≥ cN2a and who convert to negative after NST (ycN0), should undergo ALND.

Little controversy exists around the need for ALND when patients are found to have extensive axillary disease after treatment (at least 3+ positive axillary lymph nodes). In cases where patients have 1-2 positive sentinel lymph nodes at the time of definitive surgery however, considerable debate also surrounds whIch axillary surgical technique would be most appropriate. Historically, ALND was the treatment of choice when positive lymph nodes remained in the axilla following NST. Some of the guideline development groups believe that ALND can be avoided in these patients if RT has been planned postoperatively (102,104). The Eastern Health BDSG recommends that the candidates eligible for SLNB in this clinical situation should be presented at the multidisciplinary tumor board for discussion. A joint decision by the surgeon and the patient will determine which surgical technique will be implemented.

Breast Reconstruction (Upfront or Delayed)
Oncoplastic or reconstructive surgery needs to be discussed and planned in a multidisciplinary breast tumor board to determine whether the patient would be a candidate for upfront (at the time of definite surgery) or delayed reconstruction (after a time interval). The use of NST is commonly implemented when the tumor-to-breast ratio is unfavorable for these patients. The decision of which type of reconstruction (either heterologous or autologous) to be utilized is often affected by whether the patient requires postoperative RT to the chest wall (103). Oncoplastic surgery can also involve procedures to the contralateral breast to achieve symmetry.

Radiation Therapy
Radiation therapy (RT) has been found to decrease the risk of loco-regional recurrence and improve survival, and usually is indicated by the initial clinical stage and the extent of pathological disease after definitive surgery. However, the introduction of NST can change the extent of pathological disease quite dramatically which results in the initial clinical staging alone determining whether radiation therapy is warranted (60).

For those patients for whom the goal of NST was BCS, post-surgical whole breast irradiation (WBI) remains the standard of care for optimal outcomes (99). The required dose are often provided using hypofractionated RT schedules. Accelerated partial breast irradiation may be appropriate for a select population of older women with breast cancers having a low-risk of recurrence. Most guidelines also agree that boost RT should be given to the tumor bed of breast cancers having unfavourable risk factors such as premenopausal patients, grade 3, HER2-positive, TN, and an extensive intraductal component (EIC)(100). In addition to radiating the chest wall, regional nodal irradiation (including axillary, internal mammary, and supraclavicular lymph nodes) reduces the rate of breast cancer recurrence (101). Therefore, most guideline organizations recommend regional nodal irradiation (RNI), as part of the RT plan in cases where axillary lymph nodes are involved. RNI is also recommended when a mastectomy with positive lymph nodes has been performed. RNI is generally not recommended in those patients who have undergone BCS having smaller breast tumors and negative axillary lymph nodes unless tumor location or the presence of high risk features warrant it. This is also true for those who have undergone a mastectomy.

St. Gallen's recommended that radiation oncologists should use caution when attempting to tailor RT according to the patients' response to NST (103). This is mainly due to the lack of subgroup analyses on post-mastectomy radiation therapy (PMRT) studies which can clearly define specific low-risk groups post-NST. Patients eligible for PMRT after receiving NST can be presented at the multidisciplinary breast tumor board for discussion on treatment options. Presently, there are two clinical trials (NSABP B-51/RTOG 1304 and ACTO A011202 clinical trials) being conducted which may help determine whether more or less treatment is appropriate in the previous clinical situations. The NSABP B-51/RTOG 1304 trial randomized patients to either PMRT with RNI or no RT at all, in those that presented one or more positive sentinel lymph nodes which converted to negative after receiving NST, and comparing the recurrence-free intervals of each.

Recommendations:

The following recommendations of the Eastern Health Breast Disease Site Group apply to patients with a pathologically confirmed cancer of the breast who are candidates for neoadjuvant treatment:

- All patients deemed eligible for NST must have a pathologically confirmed invasive or inflammatory breast cancer.
- Whenever possible eligible patients should be presented at a multidisciplinary tumor board.
- Assessment includes:
    - Detailed medical and family history and a thorough physical examination which includes an assessment of the breast and axillary region, as well as tumor measurement.
    - Prior to treatment, full breast imaging is required, including bilateral diagnostic mammography with magnification and compression as needed, and ultrasonography as indicated.
    - A tissue marker or radiological clip should be inserted in the center of the tumor bed prior to commencement of therapy.
    - Core biopsy(s) should be taken from all suspicious findings in the breast and an FNA or core biopsy from suspicious axillary findings. Breast specimens should undergo pathology review for tumor histology as well as tested for molecular biomarkers.

  - Magnetic resonance imaging (MRI) of the breast is recommended to monitor treatment response and can be ordered by the surgeon or family physician to prevent delays in starting NST.
  - Complete blood count as well as renal and liver function blood tests.
  - Disease staging using computing tomography (CT) of chest and abdomen.
  - Bone scan, as well as a multigated acquisition scan (MUGA) as needed.
  - Fluorodeoxyglucose positron emission tomography (FDG PET) is optional and may be indicated when the presence of distant metastases is in question or for those diagnosed with inflammatory breast cancer.
  - Assessment for distress.
  - Fertility counseling where appropriate.
  - Genetic counseling if patient is at risk of hereditary breast cancer.
- All patients eligible for NST should be offered therapy according to the molecular subtype of their individual breast cancer. Therefore, patients with 'true' Luminal A tumors should be offered NET while all other patients should be offered neoadjuvant chemotherapy (combination where possible) according to molecular subtype.
- For the purposes of neoadjuvant treatment options, tumors that have both ER and PR expression in more than 50% of the nuclei on IHC assays and classified as low grade with no HER2 amplification will be considered to be luminal A subtype.
- Tumors with IHC of 1% to <10% ER staining are "low positive" expressors and are highly unlikely to respond clinically to neoadjuvant endocrine therapy. Therefore, patients whose tumors have less than 10% ER expression, will **not** be offered neoadjuvant endocrine therapy, unless pre-existing co-morbidities or advanced age preclude the use of chemotherapy.
- Until a reliable Ki-67 labeling index assessment is available, histological grade may be used in making the distinction between luminal A and luminal B subtypes.
- Neoadjuvant trastuzumab or a biosimilar agent, in combination with chemotherapy agents, should be offered to all eligible patients who have a pathological diagnosis of breast cancer, with node-positive or high-risk node negative (tumor size > 1cm) disease, and are confirmed HER2 positive, followed by adjuvant trastuzumab (or a biosimilar agent) therapy alone for duration of 1 year.
- Clinical assessment of the breast, including breast imaging, is essential during treatment to monitor for response. Breast MRI is often useful in patients, mid-treatment, when clinical response is unclear or at treatment completion to aid in the assessment of the extent of response. However, breast MRI is only helpful if one has been performed prior to commencement of treatment.
- A pCR is a desired and potential result of NST. Radiological clip placement is a highly effective way of mapping the original tumor site for an accurate assessment of the treatment response following defintive surgery. The surgeon may also ask, pre-treatment, for one or more radiological clips be inserted into the periphery of the tumor as well. Those diagnosed with multifocal breast cancer, are recommended to have clip placement in the primary tumor as well as, any satellite lesions.
- Only patients who have complete pathological eradication of all invasive and noninvasive cancer in both the breast and the axillary nodes should be considered as having a pCR, staged as ypT0ypN0.
- If little or no response is confirmed after 2 - 3 cycles of the chosen chemotherapy, the options include offering an alternate chemotherapy regimen, or if operable then patients can proceed directly to surgery, or if inoperable, neoadjuvant radiation therapy may be offered, or if neither

surgery or neoadjuvant radiation therapy are an option, the alternative may be to initiate locoregional radiation therapy with a palliative approach.

- Breast surgery after NST should be planned no later than 3 - 6 weeks after the final neoadjuvant chemotherapy cycle. A modified radical mastectomy is standard of care for those with inflammatory breast cancer. Some patients with inoperable breast cancer will also require a mastectomy. However, the goal for patients with operable and inoperable breast cancer is BCS, with an optimal margin status of “no ink on tumor”.
- Patients with inoperable breast cancers often require locoregional RT and should be presented at the multi-disciplinary tumor board, on a case-by-case basis, if BCS is being considered.
- Sentinel lymph node biopsy is standard of care for patients, with operable breast cancer who presented with a clinically and ultrasound-proven negative axilla, who are suitable for NST and BCT.
- There is some evidence to suggest that SLNB can also be an option for those patients who initially presented with positive axillary nodes (cN1) and converted to negative after NST. The choice to proceed with a SLND in this situation will depend upon a joint decision between the patient and surgeon.
- In cases where patients have 1-2 positive sentinel lymph nodes at the time of definitive surgery and wish to have a SLNB, should be presented at the multidisciplinary tumor board for discussion;
- To identify biomarker discordance, biomarkers should be retested on all definitive surgical breast cancer specimens, where possible, except in cases where the ER/PR/HER2 results were all positive on the core biopsy. Any new positive biomarker result on the definitive specimen allows breast cancer patients to avail of a more appropriate treatment option.
- Radiotherapy is indicated for all node-positive patients after NST and for all patients with locally advanced or inflammatory breast cancer. Radiotherapy may also be offered for node-negative patients depending on initial clinical stage and whether BCS was performed.
- The Eastern Health Breast Disease Site Group strongly encourages patients to enroll in available clinical trials.

Search Strategy:

Literature searches were conducted in PubMed, Embase, and the Cochrane Library, using keywords “neoadjuvant therapy” AND “breast neoplasms/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 after the year January 31, 2014 (unless the selection was an earlier landmark study) up to November 30, 2019. The inclusion/exclusion process consisted of selecting guidelines from reputable cancer organizations with preference given to those from Canadian sources where possible. Twelve source guidelines were identified and conformed to our search criteria, from which eight were selected due to currency and quality of content (102-109).

The eight identified source guidelines (102-109) were put through the ADAPTE process (110) with an AGREE II assessment (111), and the National Comprehensive Cancer Network’s “Breast Cancer” guideline was chosen to be adapted for use in our guideline (102). The 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. Joy McCarthy MD FRCPC, Dr. H. Bliss Murphy Cancer Center, St. John's, NL; Telephone 709-777-7805. 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

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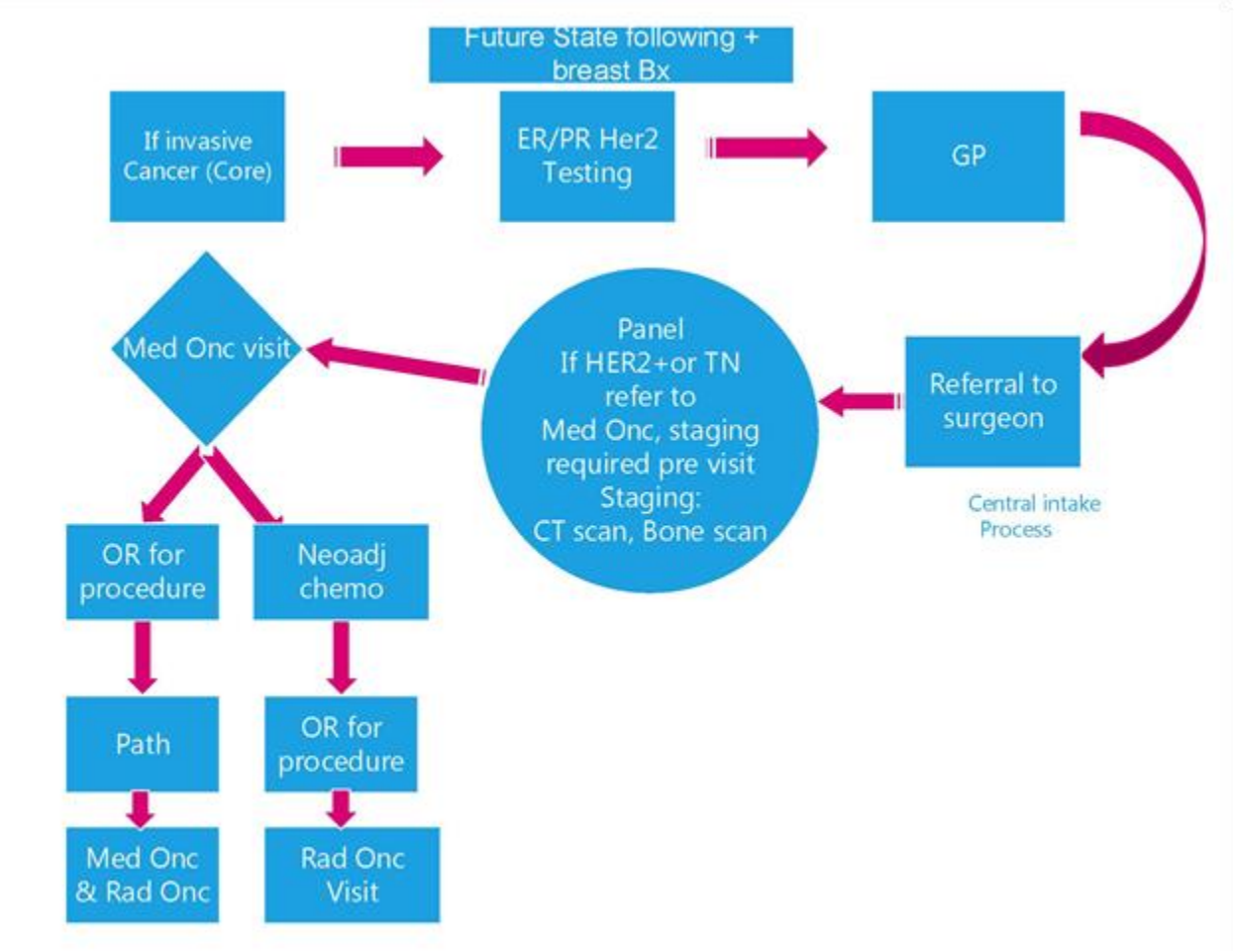
Glossary:

AGO:	Arbeitsgemeinschaft Gynäkologische Onkologie Breast Group (German)
ALND:	Axillary lymph node dissection
ASCO:	American Society of Clinical Oncology
BCS:	Breast conservation therapy
BRCA:	Breast cancer susceptibility gene such as BRCA1 and BRCA2 mutations
CAP:	College of American Pathologists
CISH:	Chromogenic in situ hybridization
CT:	Computed tomography
DCIS:	Ductal carcinoma in-situ
DFS:	Disease-free survival
ER:	Estrogen receptor
FDG PET:	Fluorodeoxyglucose positron emission tomography
FISH:	Fluorescence in situ hybridization
HER2 *neu*:	Human epidermal growth factor receptor 2 neu
IBC:	Inflammatory breast cancer
IHC:	Immunohistochemistry
ISH:	Inform HER2 dual in situ hybridization
LABC:	Locally advanced breast cancer
MRI:	Magnetic resonance imaging
MRM:	Modified radical mastectomy
NET:	Neoadjuvant endocrine therapy
NST:	Neoadjuvant systemic therapy
OS:	Overall survival

pCPA:	pan-Canadian Pharmaceutical Alliance
pCR:	pathological Complete response
PFS	Progression-free survival
PMRT:	Post-mastectomy radiation therapy
PR:	Progesterone receptor
RECIST:	Response Evaluation Criteria In Solid Tumors
RFS:	Recurrence-free survival
RNI:	Regional nodal irradiation
SERMs:	Selective estrogen receptor modulators
SLNB:	Sentinel lymph node biopsy
T-DM1:	Trastuzumab emtansine
TN/TNBC:	Triple negative or triple negative breast cancer

APPENDIX

NL Breast Cancer Care Pathway



AJCC Breast Cancer Staging

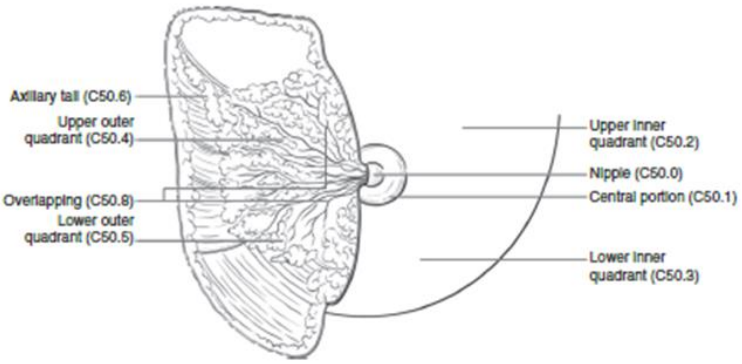


Fig. 48.1 Anatomic sites and subsites of the breast

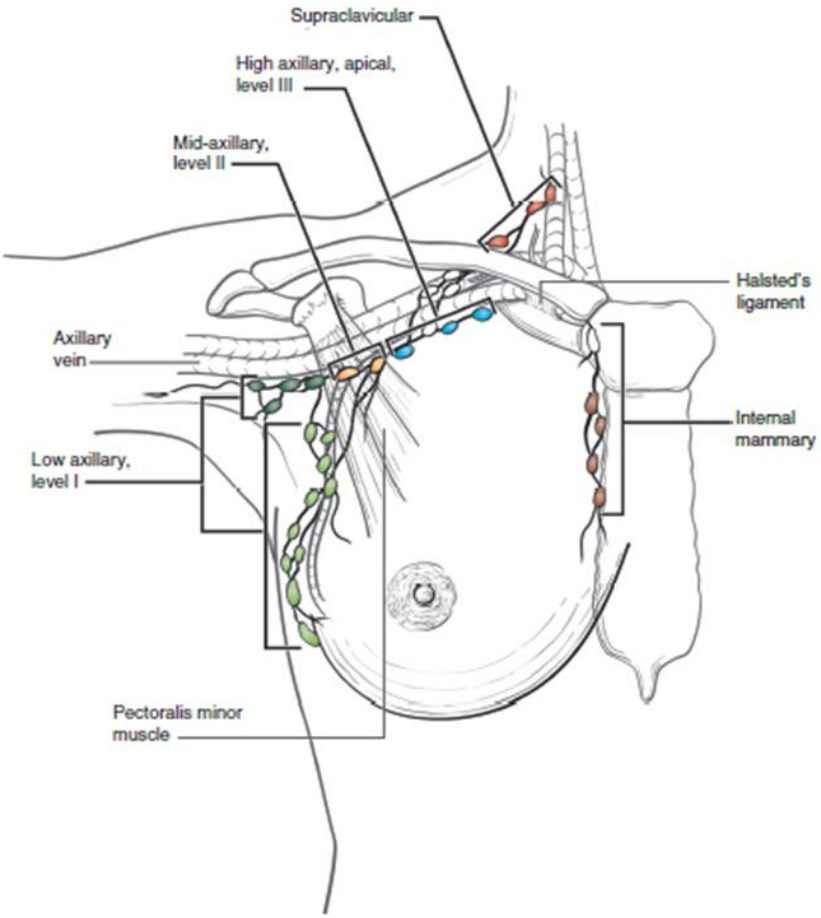


Fig. 48.2 Schematic diagram of the breast and regional lymph nodes

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).