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Clinical Practice Guidelines - Breast Disease Site

Guideline Title:	Neoadjuvant Treatment of Primary Breast Cancer	**Date:** **(O):** **(R):**	Jan 31, 2014
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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, where breast conservation therapy (BCT) may be considered. Neoadjuvant systemic therapy (NST) is the administration of pharmaceutical agents, prior to the definitive surgical procedure potentially followed by radiation therapy and 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, and has been shown to potentially improve survival, local control and operability. Multidisciplinary evaluation and planning are crucial in the use of NST to ultimately improve patient outcomes.

Questions:

1. What determines the best neoadjuvant treatment regimens for patients with pathologically confirmed breast cancer?

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

Target Population:

These recommendations apply to patients with a pathological confirmed diagnosis of 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 (NAC) 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 NAC had more favourable outcomes than those who didnot (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): A recent meta-analysis (2012), conducted on behalf of the German Breast Group and Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Breast Group, reviewed the impact of NAC on pCR and called for a standardized definition for pCR. It revealed inconsistencies in the definition of a pCR, whereby some trials define a pCR as complete resolution of the breast tumor only, while others included resolution of axillary adenopathy as well. Also, some studies included patients with focal invasive residual cancer or noninvasive residual cancer in their definition of pCR, while others defined pCR as complete eradication of all invasive and noninvasive cancer. The analysis found that the subgroup of patients who had even minimal residual disease (i.e. ypTis, ypT1mic, and ypN positive) were at increased risk of relapse as compared to patients with stage ypT0ypN0. Therefore, the recommendation of this working group was to define a pCR as the complete eradication of all invasive and noninvasive cancer in both the breast and axillary nodes (3).

Molecular Breast Cancer Subtypes

Breast cancer is a heterogeneous disease and the probability of survival appears to depend more on the combination of tumor markers 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) overexpression, and triple negative/basal-like, as per Table 1 below (4,5).

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 anti-monoclonal therapy for those subgroups with HER2 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) (4). 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 ER negative subtypes were worse. In all HER2 overexpressing tumors, women with the ER negative/PR negative/HER2 neu positive 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 (4,5). Two large randomized studies of the adjuvant use of trastuzumab among HER2 positive patients have revealed a relative improvement in DFS of 46% and 52% respectively, making adjuvant trastuzumab the standard of care in treating HER2 positive disease (6,7). TN breast cancers are now considered to have the poorest prognosis and the highest likelihood of relapse of all breast cancer 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 oncogene, are believed to receive little or no added benefit from chemotherapy, when compared to endocrine therapy alone (8-10). Neoadjuvant endocrine therapy (NET) has often been used to treat locally advanced, hormone receptor positive breast cancer in the elderly and patients for whom chemotherapy is contraindicated, or for those with a more favorable pathology i.e. pure lobular carcinoma, tubular, or low-grade mucinous tumors. However, it may also be an option for younger, fit patients with the luminal A subtype.

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, accompanied by a higher expression of proliferative genes, which accounts for its poorer long term outcomes (11,12). Ki67 is a nuclear marker of cell proliferation where higher levels are associated with worse outcomes in these breast cancer (13). 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 (13,14).

The **HER2 neu** subtype has an overexpression of HER2-related genes. Approximately 50% of all HER2 positive breast cancers also have low to negative expression of ER-related genes (15). In general, ER negative tumors are associated with higher pCR compared to ER positive tumors after NAC. A recent retrospective phase II analysis looking at pCR after NAC (in combination with trastuzumab or lapatinib or a combination of both), found that only 15% of patients with hormone receptor positive/HER2 positive breast cancer experienced a pCR compared to 29% of patients with hormone receptor negative/HER2 positive breast cancer ($p< 0.001$) (16). Other studies of HER2 positive breast cancers have also shown substantially higher rates of pCR in the hormone receptor negative group versus the hormone receptor positive one, which supports this finding (17-20).

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 (21). TN breast cancers are characterized by rapid growth with a high recurrence rate and short interval between recurrence and death. Most breast cancers with a

BRCA1 mutation have a TN/basal-like phenotype (22). However, many TN breast cancers are very sensitive to chemotherapy and tend to have higher rates of pCR then luminal subtypes (23).

Molecular Subtype Cutoffs

ER/PR: St Gallen (2005) guidelines introduced three categories for scoring ER status: endocrine responsive (strong ER expression); endocrine response uncertain (low expression of ER); and endocrine nonresponsive (no expression of ER). Although no exact cutoff to differentiate between strong and low expression was provided, the St. Gallen guidelines did suggest that tumors with 1- 9% positive cells are “usually considered” as low ER expression (24). Later, in 2009, the St. Gallen guidelines were revised to indicate that endocrine responsiveness would be defined as the presence of any detectable ER (25). 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 (26). 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, recent research out of the U.S. was published looking at the effect of the ASCO/CAP guideline for determining ER status in relation to the molecular subtyping of breast cancer (27). It compared clinicopathological characteristics between ER negative, ER positive, and low-ER staining (1-10%) tumors using chi-square analysis with $p < 0.05$ defining statistical significance. As well, gene expression profiling was carried out using the patient cohort from the Clinical Breast Care Project (CBCP) over a 10-year period, starting in 2001. All of the low-staining tumors with ER staining < 10% were found to be either basal-like (73%) or HER2 overexpressing (27%). This study reported that the ASCO/CAP threshold of ≥ 1% of stained cells defining ER positive status did not accurately reflect the underlying molecular behavior of the tumor, and in fact using this threshold of defining positivity only classified 12% of low-staining tumors correctly. An early meta-analysis of the Early Breast Cancer Trialists’ Collaborative Group looked at 55 clinical trials which demonstrated that tamoxifen use in patients with “ER-poor” tumors (0 to low expression of ER) did not provide either short- or long-term benefit (28). The importance of correctly determining ER status is paramount then to the appropriate treatment of the patient with breast cancer. Therefore, Deyarmin et al recommends that those tumors with ER staining of 1- 9% should be classified as ER negative and thus may not benefit from endocrine therapy, and that a more accurate threshold for ER positive status would be at least 10% of positive staining cells. These researchers also suggest when assessing ER status, the actual percentage of ER positive cells be recorded, so special consideration can be paid to patients with ER staining values of 1- 9%, whose tumors may not respond to endocrine therapy (27).

A recent retrospective study out of the MD Anderson Cancer Centre, evaluated outcome and response to hormone treatment in a larger number of patients with low ER staining, including 897, 241, and 119 tumors with 0%, 1-5%, and 6-10% ER staining respectively (29). This study revealed similar data to the previous study, in that clinicopathological characteristics again did

not differ significantly between the groups, except patients with 0% staining had a higher frequency of high-grade tumors. This study found that the addition of endocrine therapy to patients with low ER/PR expression (1%-10%) did not appear to have a significant effect on survival outcomes compared to patients with ER/PR < 1%.

The Eastern Health Breast Disease Site Group acknowledges the latest ASCO and St Gallen guidelines, but the expert consensus of the working group 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 amplification (30,31).

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 (32). However, this group did recognize the inter-laboratory variability of validity in methods of assessment. Currently, Ki67 testing is not available in this province. The St. Gallen international expert consensus of 2011, notes 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-) subtypes (10).

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 FISH (fluorescence in situ hybridization: ratio of HER2 gene copies to chromosome 17 centromers > 2.2) or by CISH (chromogenic in situ hybridization: more than 6 HER2 signals per cell) to determine if gene amplification was present (31,33). However, the most recent technology in HER2 testing is in use at Eastern Health, known as the Inform HER2 Dual In Situ Hybridization (ISH) test, which offers quicker and more precise results (34,35).

For the purposes of this guideline, the molecular categories and biomarker subtypes as well as the Eastern Health Breast Disease Site Group’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 Ki67 (or high grade tumors)
HER2 neu positive	ER negative and PR negative (< 1%) or ER and PR uncertain (1% - 9%), HER2 positive
Triple Negative/Basal-like	ER negative and PR negative (< 1%) or ER and PR uncertain (1% - 9%, HER2 negative

Neoadjuvant 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 may also be utilized as per Eastern Health's "Indications for Use of Breast Magnetic Resonance Imaging (MRI)" guideline (36). Baseline imaging also evaluates the presence of multifocal or multicentric disease, as well as screens for malignancy in the contralateral breast (37). During the imaging procedures, core needle biopsies of all suspicious lesions should be performed. An ultrasound of the axillary lymph nodes should also be carried out to assist in staging the axilla, and a biopsy of any suspicious findings should be done.

Breast Imaging 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. NAC 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 (37,38). An M. D. Anderson Cancer Center retrospective review has often been reported as evidence to support the use of these radiopaque markers (39). In this study, 410 nonmetastatic breast cancer patients who had undergone antracycline-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 (39).

Clinical assessment of the breast, including breast imaging, is essential during treatment to monitor for response. Breast MRI may be useful in some patients, mid-treatment, when clinical response is unclear or at treatment completion to aid in the assessment of the extent of response, but only if a breast MRI had been performed prior to commencement of treatment.

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 (anthracyclines and taxanes concurrently or sequentially for at least 6 cycles). All chemotherapy provided neoadjuvantly should be given prior to surgery rather than divided into preoperative and postoperative phases (40). 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 (41-43).
The introduction of trastuzumab, a recombinant humanized monoclonal antibody which targets HER2, in combination with chemotherapy, has revolutionalized the treatment of HER2 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 (44-48). 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 positive tumors, every 3 weeks (49). The HER2 positive cohort was compared to the HER2 negative one which revealed a pCR of 31.7% and 15.7%, respectively.
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 (50). 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 (51-54). 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) (55).

There are few clinical trials which have done a head-to-head comparison of NET to NAC. 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+ breast cancer, irregardless of HER2 neu status, and who were ineligible for BCT from the onset (56). It found at 3 months no statistically significant difference in overall objective response between the two groups. Although more patients were eligible for BCT 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 (40,57).

Research on the efficacy of other targeted agents in the neoadjuvant treatment of breast cancer, such as bevacizumab, pertuzumab and lapatinib, are ongoing.

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; • aromatase inhibitor such as anastrozole, letrozole, or exemestane for postmenopausal patients; OR Neoadjuvant Chemotherapy (NCT) 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 positive (NCT options): • taxane, a platinum such as carboplatin, and trastuzumab (trastuzumab 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 (trastuzumab 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 (trastuzumab 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 (trastuzumab 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 negative (NCT 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 positive (NCT option): • taxane, a platinum, and trastuzumab (trastuzumab will continue alone once chemotherapy is completed for a duration of 1 year);* • antimetabolite fluoropyrimidine, an anthracycline and an alkylating agent, followed by a taxane and trastuzumab (trastuzumab 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 (trastuzumab 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 (trastuzumab will continue alone once chemotherapy is completed for a duration of 1 year).*
Triple Negative, Basal-like	ER negative, PR negative, HER2 negative (NCT 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.*

**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. Pre-treatment photographs of the affected breast(s) may also be helpful. Clinical assessment of the breast, with tumor measurement, should be carried out prior to each cycle of chemotherapy (usually every 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 1 – 2 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 (if a pre-neoadjuvant therapy MRI had been performed). If the patients' tumor is determined to be a non-responder, alternate treatment regimens may be offered such as surgery or radiation therapy.

Neoadjuvant Systemic Therapy (NST) and Inoperable Breast Cancer

Historically, 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 trastuzumab. 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 (58).

Locally advanced breast cancer (LABC) is any primary tumor greater than 5 cm in diameter 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. The American Joint Committee on Cancer Staging Manual considers locally advanced breast cancer to be those with stages IIIA (T0N2M0, T1N2M0, T2N2M0, T3N2M0), IIIB or IIIC breast cancers (59). LABC is a heterogeneous disease which may include a range of all of the molecular subtypes. It is more likely to have substantial nodal involvement with an overall survival rate at 5 years of approximately 50% (60). Modified radical mastectomy (MRM) is the standard of care for patients with LABC, but BCT may be an option for a small subset of patients who desire it. These cases require presentation at a multidisciplinary tumor board for further discussion. Patients with multicentric breast cancers are not eligible for BCT.

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 (61). 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 be misdiagnosed as mastitis leading to delay in appropriate diagnosis and treatment. IBC is associated with a poor prognosis having one study report an average 5-year OS rate of 4% for patients treated with mastectomy with or without radiation (62). IBC tumors tend to have a higher incidence of both negative ER and PR status and an overexpression of HER2 than non-IBCs (63,64). Multimodality treatment with combination neoadjuvant chemotherapy has improved outcomes, which an international expert panel on IBC recommends should include an anthracycline and a taxane, followed by surgery and radiation (65). When IBC is found to be HER2 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 of trastuzumab treatment, and adjuvant endocrine therapy if indicated. Modified radical mastectomy followed by radiation therapy is standard of care. BCT is not an option for patients with IBC.

Neoadjuvant Systemic Therapy (NST) and 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 (66). **Operable breast cancer** (OBC) has been defined as tumors not more than 5 centimeters in diameter, with either impalpable or palpable but not fixed, lymph nodes with no evidence of distant metastases, which includes stage IIA, IIB and IIIA (T3N1M0 only) (59,66). Those patients with multicentric lesions (more than 2 lesions in different quadrants), persistant positive margins following repeated margin resection, widespread ductal carcinoma in situ (DCIS) or microcalcifications should not be considered for BCT (67). An international expert panel stated the goals of NST in operable breast cancer were:

- to reduce mortality from breast cancer with reduced toxicity;
- to improve surgical options;
- and to acquire early information on response and biology of the disease (68).

The neoadjuvant GeparTrio Trial enrolled 2064 patients with IBC, LABC and OBC 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 (69). Therefore, selection of neoadjuvant systemic therapy should be based on molecular subtypes (hormone receptor and HER2 status) regardless of whether the tumor burden is operable or inoperable.

Challenges Involved with Neoadjuvant Therapy

Despite its advantages, the increasing use of neoadjuvant treatment in breast cancer has presented some challenges as well for the multidisciplinary team, which include:

- *Sentinel Lymph Node Biopsy (SLNB)* – used in conjunction with neoadjuvant therapy for either operable or inoperable breast cancer, has been highly controversial (ie., timing – either before or after NST; safety - local recurrence and false negative rates). However, an international expert panel recommends that SLNB can be performed post-treatment in patients, with clinically lymph node-negative, operable breast cancer who are eligible for NST(40). It also suggested that a ultrasound of the axilla may be useful in identifying pathologically-positive lymph nodes in an otherwise clinically node negative patient. The panel recommended all patients with pathological positive lymph-nodes should receive an axillary lymph node dissection (ALND) following NST, while awaiting the results of further clinical trials on this topic;

- *Pathological Complete Response (pCR)* - as defined in the afore mentioned AGO meta-analysis, reviewed the incidence and prognostic impact of pCR among breast cancer subtypes. It found that pCR is not prognostic for slowly proliferating tumors such as Luminal A and Luminal B/HER2 positive subtypes (irrespective of trastuzumab treatment), but highly prognostic for HER2 positive (nonluminal), TN and Luminal B/HER2 negative tumors (23). 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, pCR is not a useful prognostic indicator in this subgroup. However, those patients who have a poor initial response to NST will have a worse prognosis and often treatment modification after the poor response has not resulted in clinically meaningful improvements in outcomes (70,71);

- *Radiation Therapy* – 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 initial clinical staging alone determining whether radiation therapy is warranted (40). Retrospective data has confirmed that radiation therapy provides a significant benefit to patients with locally advanced or stage III breast cancer after NAC, even those who achieve a pCR, as well as those with positive lymph nodes after NAC (69,72). For those patients for whom the goal of NST was BCT, post-surgical radiation therapy is usually the standard of care. The need for radiation therapy in patients with stage II disease with one to three positive nodes or postmastectomy node-negative patients after NST has not been well studied and requires further research. These patients may be presented at a multidisciplinary tumor board for treatment decisions.

Recommendations:

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

- All patients deemed eligible for NST must have a pathologically confirmed breast cancer;
- Thorough physical examination, including assessment of the breast and axillary region as well as tumor measurement, should be performed. Pre-treatment photographs of the affected breast(s) may be helpful in assessing treatment response;
- Prior to treatment, full breast imaging, including bilateral diagnostic mammography with magnification and compression as needed, and ultrasonography. Magnetic resonance imaging (MRI) of the breast may also be used. Core needle biopsies of all suspicious lesions should be performed;
- A pCR is a desired and potential result of NST, a tissue marker or radiological clip should be inserted in the center of the tumor bed prior to commencement of therapy. 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;
- Ultrasound of the axillary lymph nodes can be helpful in staging the axilla; biopsy of any suspicious findings should be considered;
- Clinical assessment of the breast, including breast imaging, is essential during treatment to monitor for response. Breast MRI may be useful in some patients, mid-treatment, when clinical response is unclear or at treatment completion to aid in the assessment of the extent of response, but only if a breast MRI had been performed prior to commencement of treatment;
- Tumors with IHC of less than 10% ER staining 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;
- 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;

- 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;
- 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;
- Neoadjuvant trastuzumab, 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 therapy alone for duration of 1 year;
- If little or no response is confirmed after 1-2 cycles of the chosen chemotherapy, the options include offering an alternate chemotherapy regimen, initiating radiation therapy, or, if operable, proceed directly to surgery;
- Sentinel lymph node biopsy should only be considered for patients with operable breast cancer with a clinically and ultrasound-proven negative axilla, who are suitable for NST and BCT, and only performed once neoadjuvant treatment has been completed. All patients with pathologically positive axillary lymph nodes should undergo ALND as part of their definitive surgery following NST;
- BCT should be offered to eligible patients with operable breast cancer who are suitable for NST. BCT is not standard of care for patients with LABC but can be considered at a multi-disciplinary tumor board, on a case-by-case basis, at the patient's request. Patients with IBC are not eligible for BCT;
- 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;
- 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 BCT 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 2005 (unless the selection was an earlier landmark study) up to Jan 2014. The inclusion/exclusion process consisted of selecting guidelines from reputable cancer organizations with preference given to those from Canadian sources where possible. Seven source guidelines were identified and conformed to our search criteria, from which six were selected due to currency and quality of content (73-79).

The six identified source guidelines (74-79) were put through the ADAPTE process (80) with an AGREE II assessment (81), and the Up To Date "neoadjuvant therapy for breast cancer:

Rationale, pretreatment evaluation, and therapeutic options" guideline was chosen to be adapted for use in our guideline (79). The Up To Date guideline was selected as the optimal choice due to its applicability, quality and currency of content.

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

No competing or conflicts of interest were declared.

Disclaimer:

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

Contact Information:

For more information on this guideline, please contact Dr. 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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Appendix

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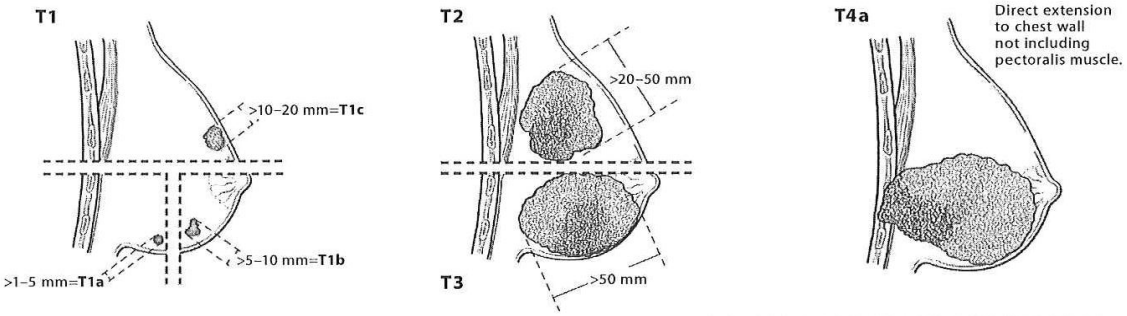
Breast Cancer Staging

7th EDITION



Primary Tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ

Tis (DCIS) Ductal carcinoma in situ

Tis (LCIS) Lobular carcinoma in situ

Tis (Paget's) Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted

T1 Tumor ≤ 20 mm in greatest dimension

T1mi Tumor ≤ 1 mm in greatest dimension

T1a Tumor > 1 mm but ≤ 5 mm in greatest dimension

T1b Tumor > 5 mm but ≤ 10 mm in greatest dimension

T1c Tumor > 10 mm but ≤ 20 mm in greatest dimension

T2 Tumor > 20 mm but ≤ 50 mm in greatest dimension

T3 Tumor > 50 mm in greatest dimension

T4 Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)

Note: Invasion of the dermis alone does not qualify as T4

T4a Extension to the chest wall, not including only pectoralis muscle adherence/invasion

T4b Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma

T4c Both T4a and T4b

T4d Inflammatory carcinoma (see "Rules for Classification")

Distant Metastases (M)

M0 No clinical or radiographic evidence of distant metastases

cM0(i+) No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases

M1 Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Notes

* T1 includes T1mi.

** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

◦ M0 includes M0(i+).

◦ The designation pM0 is not valid; any M0 should be clinical.

◦ If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.

◦ Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.

◦ Postneoadjuvant therapy is designated with "yc" or "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

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American Joint Committee on Cancer

Breast Cancer Staging

7th EDITION

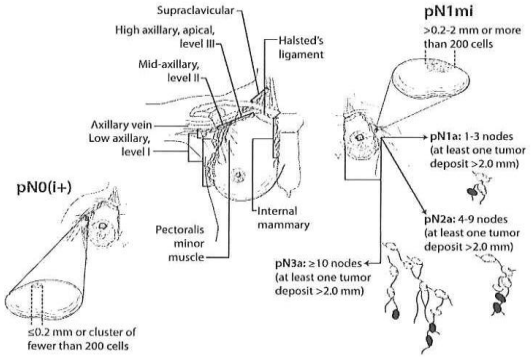
Regional Lymph Nodes (N)

CLINICAL

- NX Regional lymph nodes cannot be assessed (for example, previously removed)
- N0 No regional lymph node metastases
- N1 Metastases to movable ipsilateral level I, II axillary lymph node(s)
- N2 Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
- N2a Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
- N2b Metastases only in clinically detected* ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
- N3 Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
- N3a Metastases in ipsilateral infraclavicular lymph node(s)
- N3b Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
- N3c Metastases in ipsilateral supraclavicular lymph node(s)

Notes

* "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.



PATHOLOGIC (PN)*

- pNX Regional lymph nodes cannot be assessed (for example, previously removed, or not removed for pathologic study)
- pN0 No regional lymph node metastasis identified histologically

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

Notes

* Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(sn).

** RT-PCR: reverse transcriptase/polymerase chain reaction.

*** "Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

**** "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

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