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Clinical Practice Guidelines - Breast Disease Site

Guideline Title:	Neoadjuvant Treatment of Primary Breast Cancer - **Summary**	**Date:**	**(O):** **(R):**	Jan 31, 2014
Tumor Group:	Breast Disease Site Group	**Page:**		1 of 11
Issuing Authority:	Dr. Jehann Siddiqui Clinical Chief, Cancer Care Program	**Date Signed:**		July 4, 2014
Adapted From:	Up To Date "Neoadjuvant therapy for breast cancer: Rationale, pretreatment evaluation, and therapeutic options" guideline, April 2014 (1).			

Target Population:

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

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 neoadjuvant systemic therapy (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 pathological complete response (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 immunohistochemistry (IHC) of less than 10% estrogen receptor (ER) staining are highly unlikely to respond clinically to neoadjuvant endocrine therapy (NET). Therefore, patients whose tumors have less than 10% ER expression, will **not** be offered NET, unless pre-existing co-morbidities or advanced age preclude the use of chemotherapy;
- For the purposes of neoadjuvant treatment options, tumors that have both estrogen receptor (ER) and progesterone receptor (PR) expression in more than 50% of the nuclei on IHC assays, and classified as low grade with no human epidermal growth factor 2 receptor (HER2/neu) over-amplification will be considered to be luminal A subtype;
- Until a reliable Ki-67 (a cellular marker for proliferation) 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/neu 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 (SLNB) should only be considered for patients with operable breast cancer with a clinically and ultrasound-proven negative axilla, who are suitable for NST and breast conservation therapy (BCT), and only performed once neoadjuvant treatment has been completed. All patients with pathologically positive axillary lymph nodes should undergo axillary lymph node dissection (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 locally advanced breast cancer (LABC) but can be considered at a multi-disciplinary tumor board, on a case-by-case basis, at the patient's request. Patients with inflammatory breast cancer are not eligible for BCT;
- Only patients who have had a 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.

Supporting Evidence:

Historically, NST was first used in an attempt to make large, locally advanced breast cancers amenable to surgical removal. However, a Cochrane review also found NST to be a safe treatment option for operable (or early) breast cancer while improving the rate of breast conservation therapy (1). Some of the advantages of NST treatment for patients with inoperable breast cancer include:

- Earlier treatment of distant micrometastases;
- Downstaging of primary tumor;
- Potential for improved operability;
- Allows in vivo assessment of response to specific systematic agents (2).

The goals of NST in operable or early breast cancer are:

- 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 (3).

A 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 pCR after NAC had more favourable outcomes than those who did not (4). However, pCR has not been found to be prognostic for DFS and OS for all breast cancers when analyzed by subtype (5). Gene expression profiling studies of breast tumors have identified at least four subtypes based on ER/PR status and HER2/neu status: luminal A, luminal B, human epidermal growth factor receptor 2 (HER2) overexpression, and triple negative/basal-like (6,7). Patients with breast cancer of the luminal A or luminal B (HER2/neu positive) subtype have similar prognosis whether a pCR was achieved or not, while luminal B (HER2/neu negative), HER2/neu positive (non-luminal), and triple negative subtypes have far better outcomes with a pCR (8).

Qualifying Statements:

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

Subtype	Molecular Markers and Cutoffs
Luminal A	ER positive and PR 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

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 (9-11). 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 (12,13). Ki67 is a nuclear marker of cell proliferation where higher levels are associated with worse outcomes in these breast cancer (14). 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 (14,15).

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 (16). 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 ($p< 0.001$) (17). 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 (18-21).

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 (22). 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 (23). However, many TN breast cancers are very sensitive to chemotherapy and tend to have higher rates of pCR then luminal subtypes (24).

TABLE 2: **Neoadjuvant Systemic Therapy Regimens According to Molecular Breast Cancer Subtypes (25-41)**

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-fluorouraci (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".

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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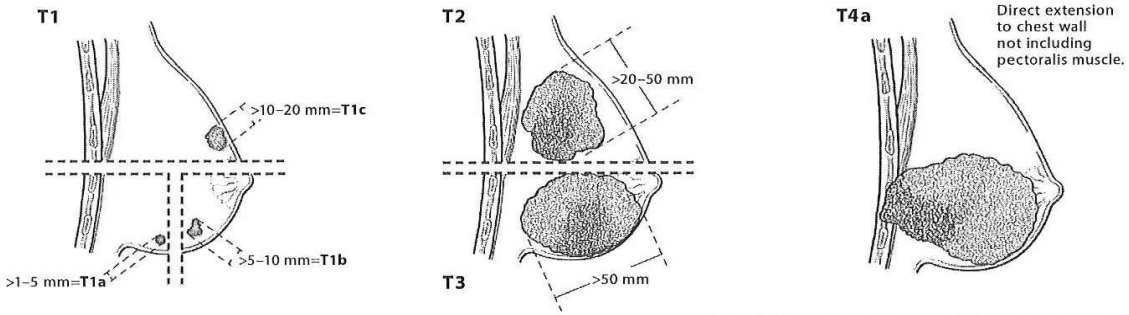
Appendix:

American Joint Committee on Cancer

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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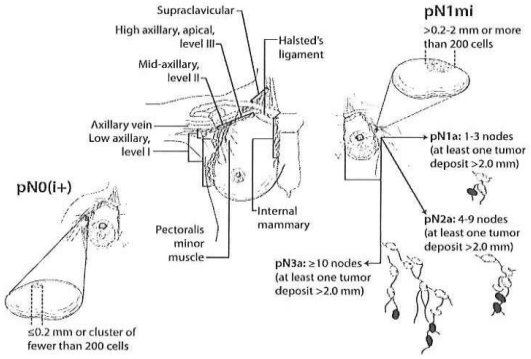
Regional Lymph Nodes (N)

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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