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Breast Cancer: Noninvasive and Special Situations

Clinical Practice Guidelines in Oncology

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Overview

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer: Noninvasive and Special Situations presented here are the work of the NCCN Breast Cancer panel members. Categories of evidence and consensus were assessed and are noted in the algorithms and text. Although not explicitly stated at every decision point of the guidelines, patient participation in prospective clinical trials is the preferred option of treatment for all stages of breast cancer. These NCCN Guidelines fo-

NCCN Clinical Practice Guidelines in Oncology for Breast Cancer: Noninvasive and Special Situations

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, noninvasive breast cancer, breast-conserving therapy, mastectomy, endocrine therapy, tamoxifen, radiation therapy, lobular carcinoma in situ, ductal carcinoma in situ *(JNCCN* 2010;8:1182–1207)

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

The full NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer are not printed in this issue of *JNCCN*, but can be accessed online at www.NCCN.org.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Guidelines Panel for Breast Cancer: Noninvasive and Special Situations

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Guidelines for Breast Cancer: Noninvasive and Special Situations panel members can be found on page 1207. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, please visit www.NCCN.org.

cus on noninvasive breast cancer and special situations, such as Paget's disease, phyllodes tumor, breast cancer during pregnancy, and axillary breast cancer. Another NCCN guideline addresses invasive breast cancer (see NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Breast Cancer: Invasive and Inflammatory; to view the complete and most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

The American Cancer Society estimates that 194,280 new cases of invasive breast cancer were diagnosed and 40,610 died of the disease in the United States in 2009.[1] In addition, approximately 62,280 women were diagnosed with carcinoma in situ of the breast during the same year. Breast cancer is the most common malignancy in women in the United States and is second only to lung cancer as a cause of cancer death.

The incidence of breast cancer has increased steadily in the United States over the past few decades, but breast cancer mortality seems to be declining,[1,2] suggesting a benefit from early detection and more effective treatment.

The origin of most breast cancer cases is unknown. However, numerous risk factors for the disease have been established, including female gender, increasing patient age, family history of breast cancer at a young age, early menarche, late menopause, older age at first live childbirth, prolonged hormone replacement therapy, previous exposure to therapeutic chest wall irradiation, benign proliferative breast disease, and genetic mutations, such as of the *BRCA1/2*

Text continues on p. 1193

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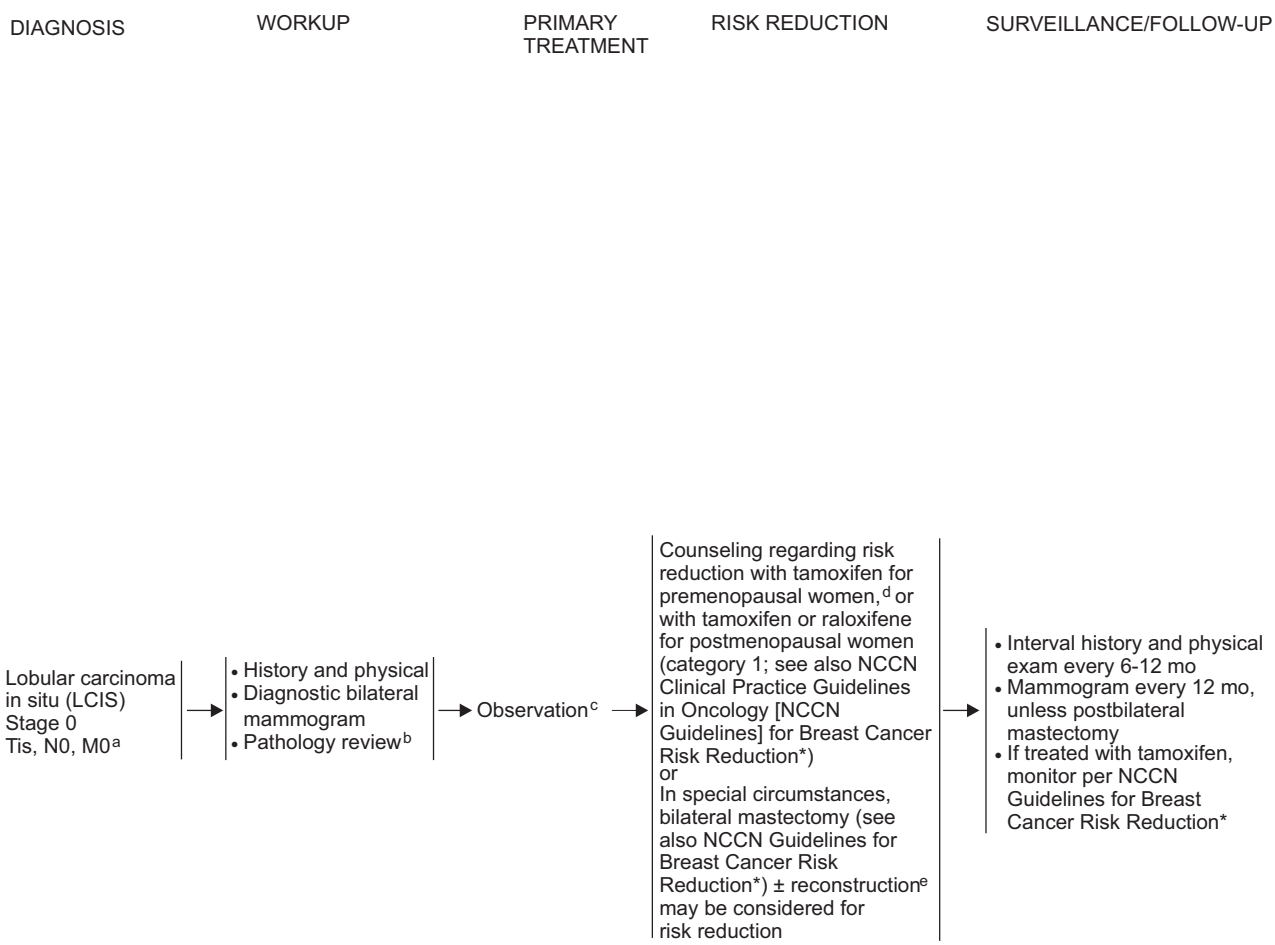

†Lobular carcinoma in situ
*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

[a]See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer Screening and Diagnosis.*
[b]The panel endorses the College of American Pathology protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast (http://www.cap.org).
[c]Some variants of LCIS ("pleomorphic LCIS") may have a similar biological behavior to that of DCIS. Clinicians may consider complete excision for pleomorphic LCIS but outcome data regarding the efficacy of surgical excision to negative margins and/or radiotherapy are lacking.
[d]Some serotonin reuptake inhibitors decrease the formation of endoxifen, an active metabolite of tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. The clinical impact of these observations is not known.
[e]See Principles of Breast Reconstruction Following Surgery (available online, in these guidelines, at www.NCCN.org [BINV-G]).

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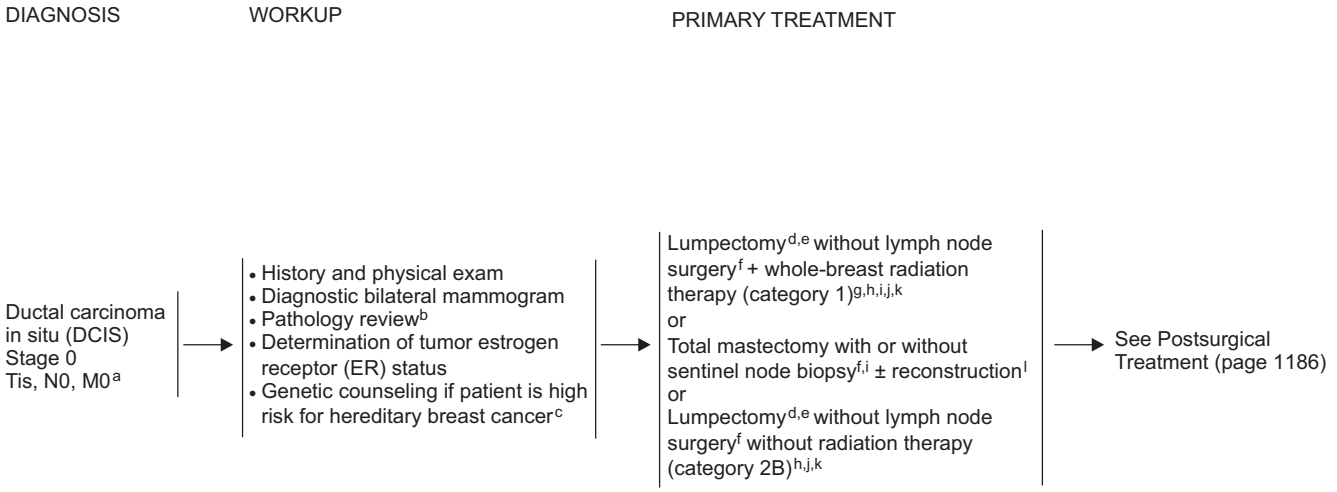

†Ductal carcinoma in situ
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[a] See NCCN Guidelines for Breast Cancer Screening and Diagnosis.*
[b] The panel endorses the College of American Pathology protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast (http://www.cap.org).
[c] See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast and Ovarian.*
[d] Re-resection(s) may be performed in an effort to obtain negative margins in patients desiring breast-conserving therapy. Patients not amenable to margin-free lumpectomy should have total mastectomy.
[e] See Margin Status in DCIS (page 1187).
[f] Complete axillary lymph node dissection should not be performed in the absence of evidence of invasive cancer or proven metastatic disease in women with apparent pure DCIS. However, a small proportion of patients with apparent pure DCIS will be found to have invasive cancer at their definitive surgical procedure. Therefore, the performance of a sentinel lymph node procedure may be considered if the patient with apparent pure DCIS is to be treated with mastectomy or with excision in an anatomic location compromising the performance of a future sentinel lymph node procedure.
[g] See Principles of Radiation Therapy (available online, in these guidelines, at www.NCCN.org [BINV-H]).
[h] Complete resection should be documented by analysis of margins and specimen radiography. Postexcision mammography should also be performed whenever uncertainty remains about adequacy of excision.
[i] Patients found to have invasive disease at total mastectomy or reexcision should be managed as stage I or II disease, including lymph node staging.
[j] See Special Considerations Breast-Conserving Therapy (available online, in these guidelines, at www.NCCN.org [BINV-F]).
[k] Whole-breast radiation therapy after lumpectomy reduces recurrence rates in DCIS by approximately 50%. Approximately half of the recurrences are invasive and half DCIS. Several factors determine that local recurrence risk, including size, tumor grade, margin status, and patient age. Some patients may be treated with excision alone, if the patient and the physician view the individual risks as "low". All data evaluating the 3 local treatments show no differences in patient survival.
[l] See Principles of Breast Reconstruction Following Surgery (available online, in these guidelines, at www.NCCN.org [BINV-G]).

DCIS POSTSURGICAL TREATMENT

Risk reduction therapy for ipsilateral breast after breast-conserving surgery:
Consider tamoxifen[m] for 5 years for:
- Patients treated with breast-conserving therapy (lumpectomy) and radiation therapy (category 1),[n] especially for those with ER-positive DCIS. The benefit of tamoxifen for ER-negative DCIS is uncertain
- Patients treated with excision alone[n]

Risk reduction therapy for contralateral breast:
- Counseling regarding consideration of tamoxifen for risk reduction (category 2B).[m] See also NCCN Guidelines for Breast Cancer Risk Reduction*

SURVEILLANCE/FOLLOW-UP

- Interval history and physical exam every 6-12 mo for 5 y, then annually
- Mammogram every 12 mo (and 6-12 mo postradiation therapy if breast conserved [category 2B])
- If treated with tamoxifen, monitor per NCCN Guidelines for Breast Cancer Risk Reduction*

†Ductal carcinoma in situ
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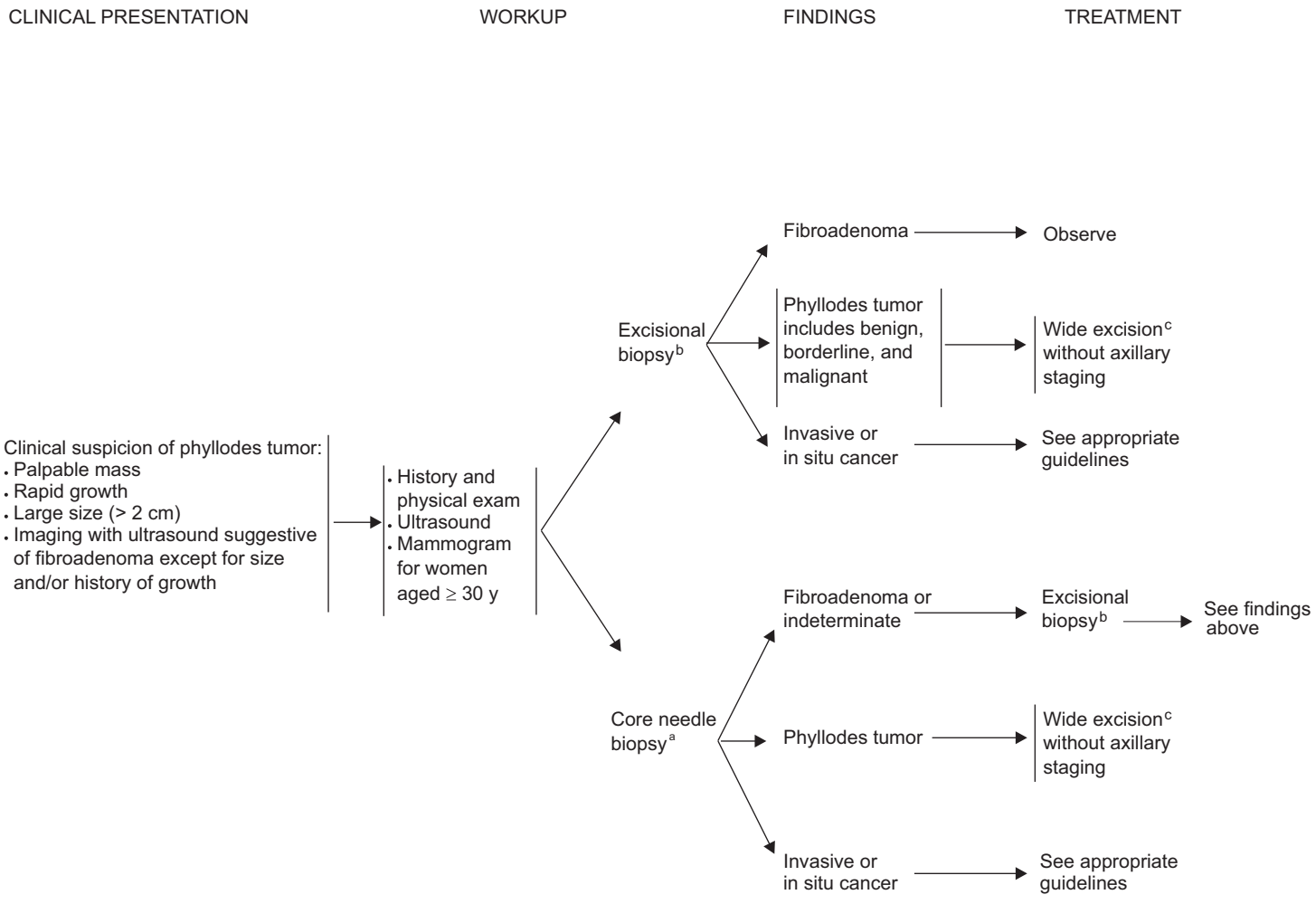
[m] Some serotonin reuptake inhibitors decrease the formation of endoxifen, an active metabolite of tamoxifen. However, citalopram and venlafaxine seem to have minimal impact on tamoxifen metabolism. The clinical impact of these observations is not known.
[n] Available data suggest tamoxifen provides risk reduction in the ipsilateral breast treated with breast conservation and in the contralateral breast in patients with mastectomy or breast conservation with ER-positive primary tumors. Because a survival advantage has not been shown, individual consideration of risks and benefits is important (see also NCCN Guidelines for Breast Cancer Risk Reduction*).

MARGIN STATUS IN DCIS

Substantial controversy exists regarding the definition of a negative pathologic margin in DCIS. Controversy arises out of the heterogeneity of the disease, difficulties in distinguishing the spectrum of hyperplastic conditions, anatomic considerations of the location of the margin, and inadequate prospective data on prognostic factors in DCIS. Margins > 10 mm are widely accepted as negative (but may be excessive and may lead to a less optimal cosmetic outcome). Margins < 1 mm are considered inadequate. With pathologic margins between 1 and 10 mm, wider margins are generally associated with lower local recurrence rates. However, close surgical margins (< 1 mm) at the fibroglandular boundary of the breast (chest wall or skin) do not mandate surgical reexcision but can be an indication for higher boost dose radiation to the involved lumpectomy site. (category 2B)

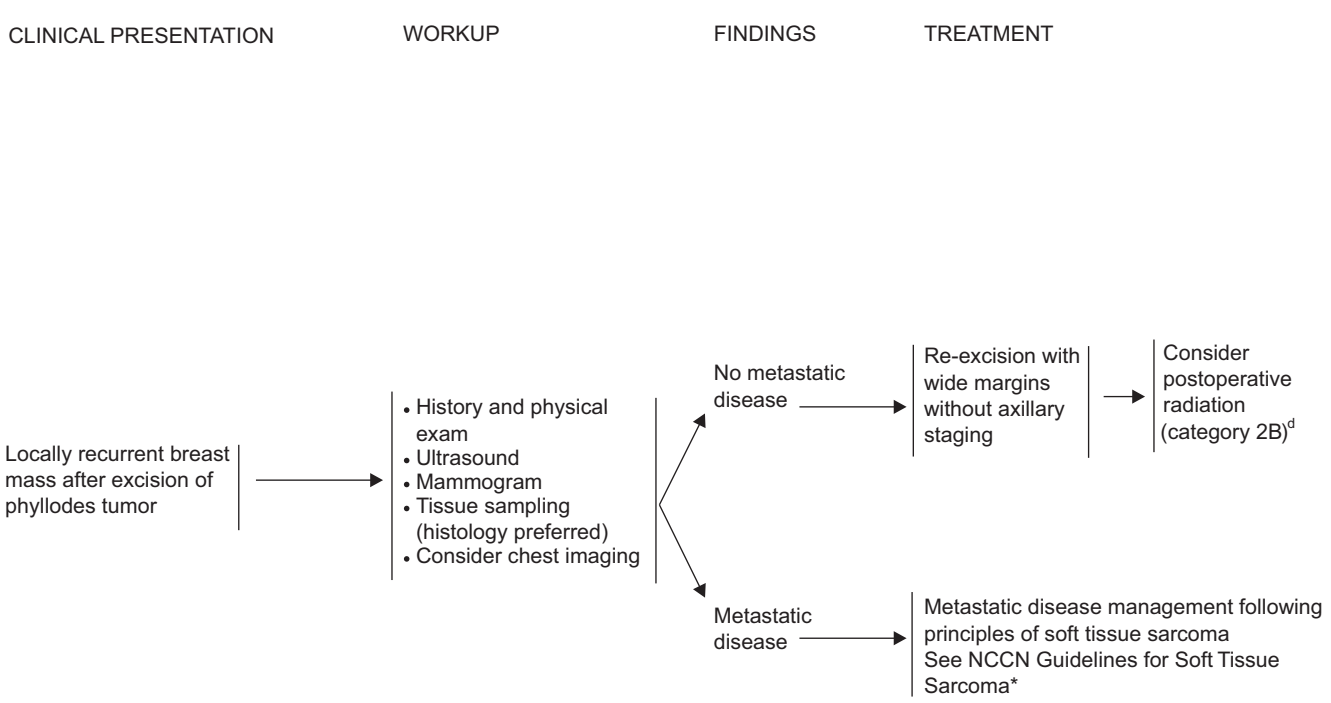
†Ductal carcinoma in situ



[a] FNA will not, and core biopsy may not, distinguish fibroadenoma from phyllodes tumor in most cases.
[b] Excisional biopsy includes complete mass removal, but without the intent of obtaining surgical margins.
[c] Wide excision means excision with the intention of obtaining surgical margins ≥ 1 cm. Narrow surgical margins are associated with heightened local recurrence risk, but are not an absolute indication for mastectomy when partial mastectomy fails to achieve margin width ≥ 1 cm.

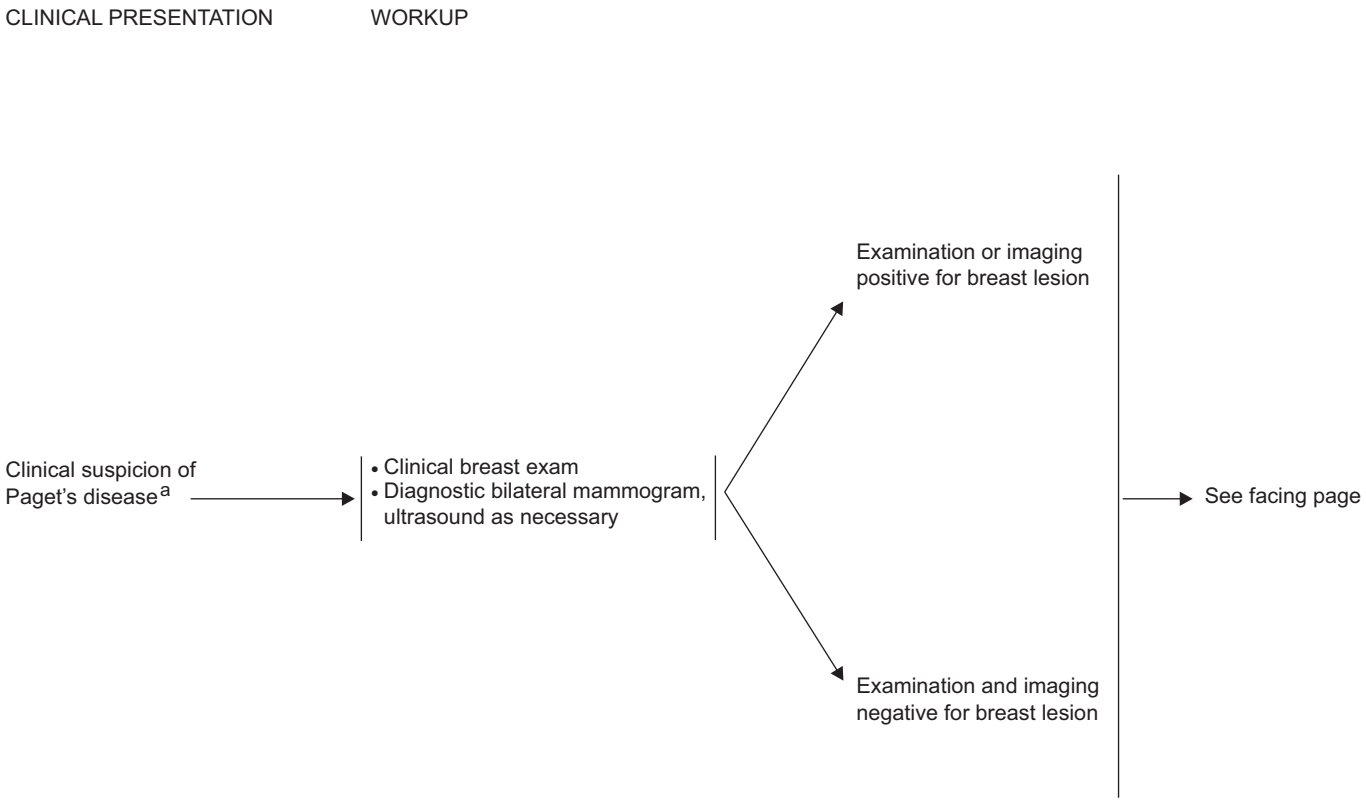
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

PHYLLODES TUMOR RECURRENCE

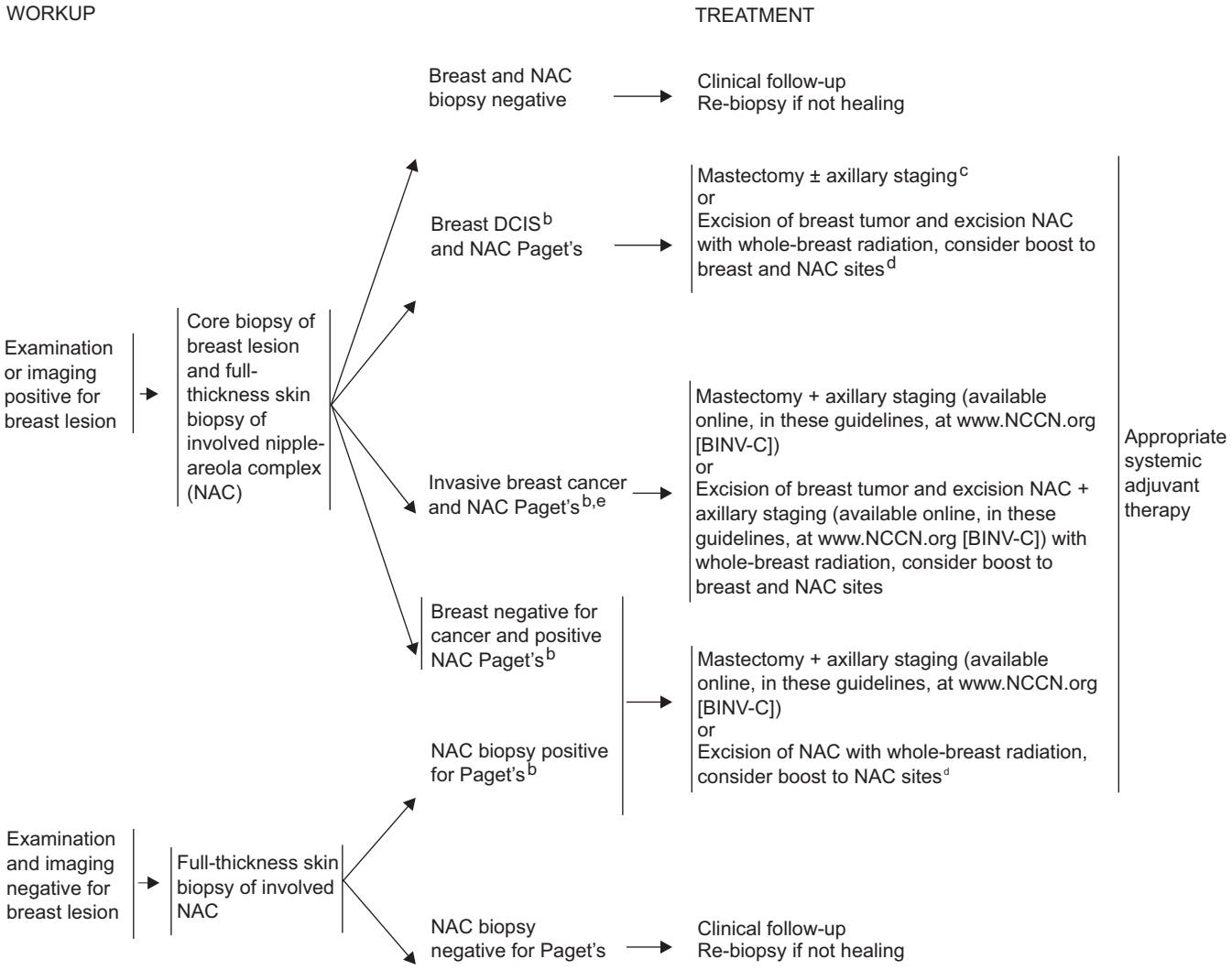


*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

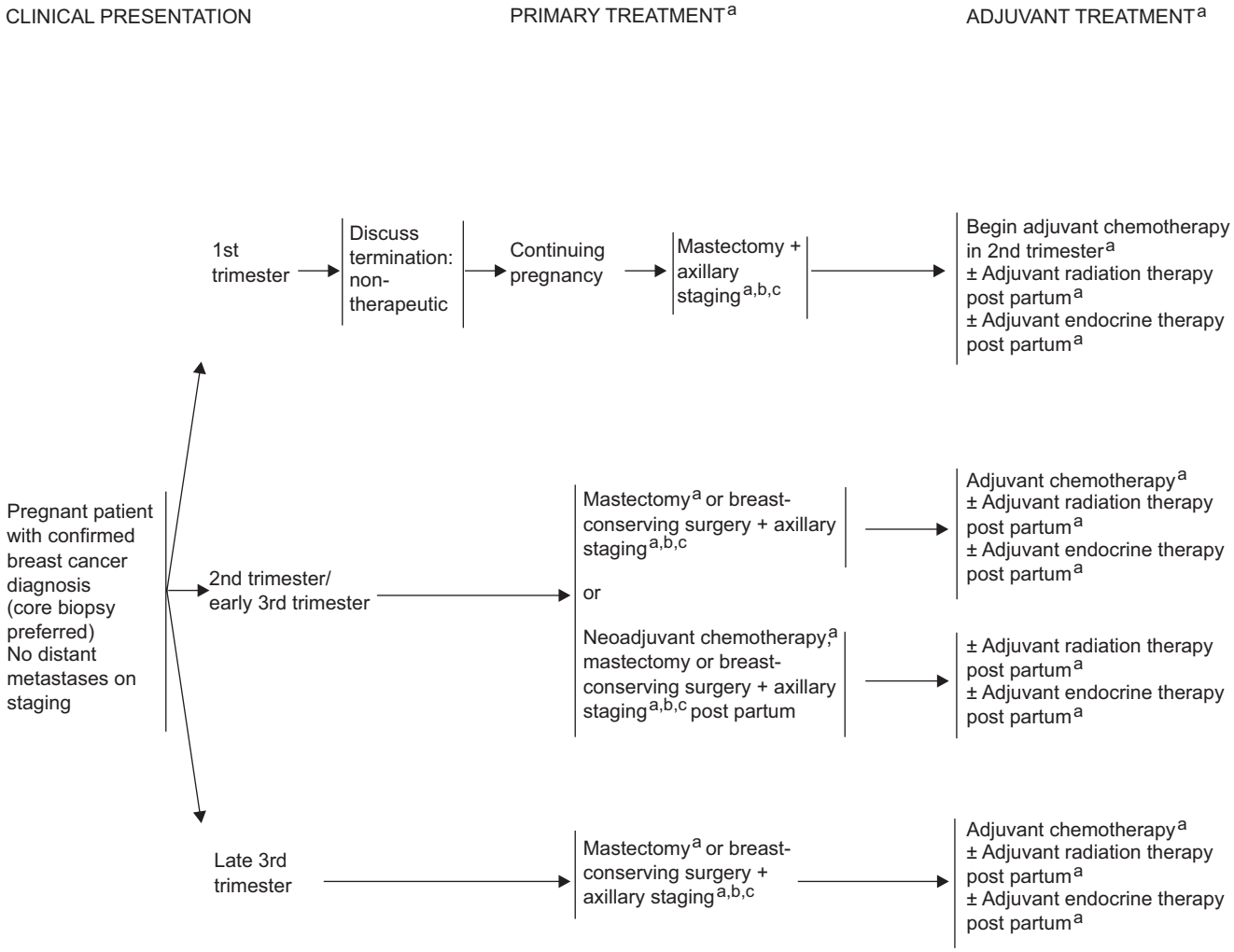
[d] No prospective randomized data support the use of radiation treatment with phyllodes tumors. However, in the setting where additional recurrence would create significant morbidity (e.g., chest wall recurrence after salvage mastectomy), radiation therapy may be considered, following the same principles that are applied to the treatment of soft tissue sarcoma.



[a]Nipple or areolar eczema, ulceration, bleeding, itching.



[b] To assess extent of disease or confirm additional disease consider MRI (available online, in these guidelines, at www.NCCN.org [BINV-B]).
[c] Mastectomy is always an option with any manifestation of Paget's disease (see manuscript text).
[d] With Paget's disease and no associated peripheral cancer, or with associated DCIS, consider tamoxifen 20 mg per day for 5 years.
[e] With associated invasive breast cancer, treat with appropriate systemic adjuvant therapy (available online, in these guidelines, at www.NCCN.org [BINV-4]).



†Breast cancer during pregnancy

[a]Considerations and selection of optimal local therapy and systemic therapy are similar to those recommended in non–pregnancy-associated breast cancer, see other sections of this guideline. However, the selection and timing of chemotherapy, endocrine therapy, and radiation therapy are different in the pregnant versus nonpregnant patient. Please see discussion section. Chemotherapy should not be administered during the first trimester of pregnancy and radiation therapy should not be administered during any trimester of pregnancy. Most experience with chemotherapy during pregnancy for breast cancer is from regimens that utilize various combinations of doxorubicin, cyclophosphamide and fluorouracil. Consideration for post-partum chemotherapy are the same as for non–pregnancy-associated breast cancer.

[b]See Surgical Axillary Lymph Node Staging (available online, in these guidelines, at www.NCCN.org [BINV-C]).

[c]Safety data are insufficient to recommend general use of taxanes during pregnancy. The use of blue dye and trastuzumab are contraindicated during pregnancy.

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genes. However, except for female gender and increasing patient age, these risk factors are associated with only few breast cancers. Women with a strong family history of breast cancer should be evaluated according to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast and Ovarian (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). Women at increased risk for breast cancer (generally those with a ≥ 1.67% 5-year risk of breast cancer according to the Gail model of risk assessment[3]) may consider risk reduction strategies (see NCCN Guidelines for Breast Cancer Risk Reduction, in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Proliferative abnormalities of the breast are limited to the lobular and ductal epithelium. In both the lobular and ductal epithelium, a spectrum of proliferative abnormalities may be seen, including hyperplasia, atypical hyperplasia, in situ carcinoma, and invasive carcinoma.[4] Approximately 85% to 90% of invasive carcinomas are ductal in origin. Invasive ductal carcinomas include unusual variants of breast cancer, such as colloid or mucinous, adenoid cystic, and tubular carcinomas, which have especially favorable natural histories.

Staging

In January 2003, the American Joint Committee on Cancer (AJCC) revised the Cancer Staging Manual (sixth edition) to incorporate important changes and additions in the TNM staging system for breast cancer (Table 1; available online, in these guidelines, at www.NCCN.org [ST-1]).[5,6] This revision differs from the 1997 edition of the AJCC staging by incorporating the increasing use of novel imaging and pathology techniques used at diagnosis (e.g., sentinel node biopsy and immunohistochemistry [IHC] evaluation of nodes) and the number of lymph nodes involved as a factor in staging allocation. The most substantial changes are:

- Micrometastases to ipsilateral axillary lymph nodes are distinguished from isolated tumor cells based on size and histologic evidence of malignant activity. All metastatic lesions to ipsilateral axillary lymph nodes no larger than 0.2 mm, whether detected using hematoxylin and eosin (H&E) staining or IHC, will be described as pN0(i+). pN0(i–) is used to indicate no detectable tumor cells using either H&E or IHC. The designation pN1mi with no additional identifiers will be used for micrometastases greater than 0.2 mm but no greater than 2.0 mm in greatest dimension.[7]
- Identifiers are added to indicate the use of sentinel lymph node resection and IHC or molecular pathology techniques.
- The number of involved nodes as determined with routine H&E staining (preferred method) or IHC staining impacts pathologic N staging (pN1 if 1–3 lymph nodes, pN2 if 4–9 lymph nodes, and pN3 if ≥ 10 lymph nodes are involved).
- Metastases to infraclavicular nodes are categorized as N3 disease.
- Metastases to internal mammary (IM) nodes impact staging according to the method of detection and presence or absence of concomitant axillary lymph node involvement (N1 disease if involved IM lymph nodes are detected exclusively using sentinel lymph node detection procedure; N2 disease if detected using any other imaging study or clinical examination; or N3 disease if concomitant axillary lymph node involvement is present).
- Metastasis to ipsilateral supraclavicular lymph nodes is no longer considered M1 disease and is classified as N3 disease.

Although determining the specific TNM status has become more complex (especially regarding lymph node staging), the allocation of specific TNM combinations to different stage groupings remains the same, except for the creation of stage IIIC to specifically identify patients with T any, N3, M0 disease. This revised staging system recognizes the heterogeneity of breast cancer and the need to create uniform data collection standards to better assess both the long-term outcome of specific patient subgroups and the impact of novel imaging or pathology techniques.[6]

Pathology Assessment

A central component of breast cancer treatment is full knowledge of disease extent and biologic features. These factors help determine the disease stage, help estimate the risk that the cancer will recur, and provide information that predicts response to therapy (e.g., hormone receptors and human epidermal

growth factor receptor 2 [HER2]). These factors are determined through examining excised tissue and are provided in a written pathology report. Accurate pathology reporting requires the clinician and pathologist to communicate about relevant patient history, prior breast biopsies, prior irradiation to the chest, pregnancy status, characteristics of the abnormality biopsied (e.g., palpable, mammographically detected, microcalcifications), clinical state of lymph nodes, presence of inflammatory change or other skin abnormality, and any prior treatment administered (e.g., chemotherapy, radiation therapy). The specimens should be oriented for the pathologist, and specific requests to determine biomarkers stated (e.g., estrogen receptor [ER], progesterone receptor [PR], and HER2 status). Use of consistent, unambiguous standards for reporting is strongly encouraged. Data from both national and local surveys show that as many as 50% of pathology reports for breast cancer are missing some elements critical to patient management.[8,9] Significant omissions include failure to orient and report surgical margins, and failure to report tumor grade consistently.

ER status should be determined for all samples of ductal carcinoma in situ (DCIS), and ER and PR status should be determined for all samples of invasive breast cancer. ER and PR status is normally determined through IHC testing. Although this method is considered reliable when performed by experienced pathology personnel, several reports indicate that the reliability of ER and PR determinations can vary widely among laboratories,[10–12] possibly because of the diverse methodologies and interpretation schema used to evaluate tumor hormonal status. An NCCN task force has reviewed this topic and issued recommendations on ER and PR testing in breast cancer.[13]

Along with ER and PR tumor status, the guidelines specify the need to determine HER2 status for all newly diagnosed invasive breast cancers. HER2 status can be assessed through measuring the number of *HER2* gene copies (using fluorescence in situ hybridization [FISH]), or using a complementary method (IHC) to assess the quantity of HER2 cell surface receptors.[14] Six methods currently are FDA-approved for determining the HER2 status of breast cancer tumors: 1) IHC HercepTest (DAKO, Glostrup, Denmark)[15]; 2) IHC Pathway HER2 test (Ventana Medical Systems, Tucson, Arizona)[16]; 3) INFORM HER2 FISH test (Ventana Medical Systems)[17]; 4) PathVysion HER2 FISH test (Vysis, Downers Grove, Illinois)[18]; 5) PharmaDX HER2 FISH test (DAKO)[19]; and 6) the SPOT-Light HER2 CISH test (Invitrogen, Carmarillo, California).[20] However, many anatomic pathology laboratories are using modifications of some of these methods.

The accuracy of HER2 assays used in clinical practice is a major concern, and results from several studies have shown that false-positive[21–25] and false-negative[21,26] HER2 test results are common. An NCCN task force has reviewed this topic and issued recommendations on HER2 testing in breast cancer[27] summarized in these guidelines online, at www.NCCN.org (BINV-A). The panel considers either IHC or FISH acceptable for making an initial determination of HER2 tumor status, provided that the test method was validated and shown to be at least 95% concordant with another validated method. Evidence for 95% concordance between the HER2 assay used and a validated complementary HER2 testing method is also required. Breast cancer tumors are classified as HER2-positive if FISH testing shows *HER2* gene amplification or if they have an IHC score of 3 or greater. The guidelines describe strategies for evaluating tumors with borderline or indeterminate HER2 status (e.g., FISH [PathVysion] scores of 1.8–2.2 *HER2* genes/chromosome 17/cell, FISH [INFORM] scores of > 4 to < 6 *HER2* genes/cell, or IHC scores of ≥ 2; available online, in these guidelines, at www.NCCN.org [BINV-A]). HER2 testing should be performed only in laboratories accredited to perform such testing. Furthermore, these laboratories should have standardized HER2 testing procedures established, and programs to periodically evaluate the proficiency of personnel performing HER2 testing. HER2 test reports must provide information such as tumor site, specimen type, histologic type, fixation method and time, block examined, testing methods used. Clinicians should be familiar with the significance of these criteria when making individual clinical recommendations.

A joint panel from ASCO and the College of American Pathologists (CAP) issued HER2 testing guidelines that are fully consistent with those recommended by NCCN, but which also provide detailed recommendations for a substantial ongoing quality assurance program for laboratory accreditation from CAP.[28] The panel endorses CAP accreditation for anatomic pathology laboratories performing HER2 testing.

CAP developed pathology reporting protocols to promote complete and standardized reporting of malignant specimens. These protocols are available for each disease site and include cancer case summaries (checklists) along with background documentation. These checklists form the basis for a synoptic, standardized reporting of pathologic findings. These checklists are available for free through the CAP Web site at www.cap.org.

Consistent, unambiguous, and complete pathology reporting is a cornerstone of quality breast cancer care, and the panel endorses use of the CAP protocols for reporting the pathologic analysis of all breast specimens.

Treatment Approach

Conceptually, the treatment of breast cancer includes the treatment of local disease with surgery, radiation therapy, or both, and the treatment of systemic disease with cytotoxic chemotherapy, endocrine therapy, biologic therapy, or combinations of these. The need for and selection of various local or systemic therapies are based on several prognostic and predictive factors, including tumor histology, clinical and pathologic characteristics of the primary tumor, axillary node status, tumor hormone receptor content, tumor HER2 status, presence or absence of detectable metastatic disease, patient comorbid conditions, patient age, and menopausal status. Breast cancer does occur in men, and men with breast cancer should be treated similarly to postmenopausal women, except that the use of aromatase inhibitors is ineffective without concomitant suppression of testicular steroidogenesis.[29,30] Patient preference is a major component of the decision-making process, especially when the available treatment options have equivalent survival rates.

In terms of treatment, breast cancer may be divided into 1) the pure noninvasive carcinomas, which include lobular carcinoma in situ (LCIS) and DCIS (stage 0); 2) operable, locoregional invasive carcinoma with or without associated noninvasive carcinoma (clinical stage I, stage II, and some stage IIIA tumors); 3) inoperable locoregional invasive carcinoma with or without associated noninvasive carcinoma (clinical stage IIIB, stage IIIC, and some stage IIIA tumors); and 4) metastatic or recurrent carcinoma (stage IV).

Pure Noninvasive Carcinomas (Stage 0)

Both LCIS and DCIS may be difficult to distinguish from atypical hyperplasia or from carcinomas with early invasion.[31,32] Therefore, pathologic review of all cases is recommended. Bilateral diagnostic mammography should be performed to identify the presence of multiple primary tumors and to estimate the extent of the noninvasive lesion. Diagnostic evaluation of LCIS is described in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer Screening and Diagnosis, and genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer as defined by the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian (to view the most recent version of these guidelines, visit www.NCCN.org). Testing for genetic mutations without formal genetic counseling is discouraged.

The goal of treatment for pure in situ carcinoma is either preventing the occurrence of invasive disease or diagnosing the development of an invasive component when still localized to the breast. Patients found to have invasive disease, even if microinvasive, on pathology review or at reexcision, mastectomy, or axillary lymph node staging should be treated according to the stage-appropriate guideline for invasive carcinoma.

Lobular Carcinoma In Situ: After a recommended workup, including history and physical examination, diagnostic bilateral mammography, and pathology review, observation alone is the preferred option for women diagnosed with pure LCIS because their risk of developing invasive carcinoma is low (~ 21% over 15 years).[33] The histologies of invasive carcinomas tend to be favorable, and deaths from secondary invasive cancers are unusual in appropriately monitored women.[34] Bilateral mastectomy, with or without reconstruction, should be considered in special circumstances, such as in women with a *BRCA1/2* mutation or a strong family history of breast cancer. Panel consensus is that a risk-reduction mastectomy can be considered as an option for women with LCIS without additional risk factors, but this approach is not recommended for most of these women. The decision to proceed with a risk-reduction mastectomy in a woman with LCIS should be made only after careful evaluation and multidisciplinary counseling (see NCCN Guidelines for Breast Cancer Risk Re-

duction, in this issue; to view the most recent version, visit the NCCN Web site at www.NCCN.org).

The risk for development of an invasive breast cancer after a diagnosis of LCIS is equal in both breasts.[35] If mastectomy is considered as a risk reduction strategy, then a bilateral procedure is required to optimally minimize risk. Women treated with bilateral mastectomy are appropriate candidates for breast reconstruction (available online, in these guidelines, at www.NCCN.org [BINV-G]).

Evidence supports the existence of histologically aggressive variants of LCIS (e.g., pleomorphic LCIS), which may have a greater potential than classic LCIS to develop into invasive lobular carcinoma.[36] However, outcome data regarding treatment of patients with pleomorphic LCIS are lacking, partly because of a paucity of histologic categorization of variants of LCIS. Therefore, the panel has not made recommendations for the treatment of pleomorphic LCIS as a distinct entity of LCIS.

Women with LCIS, whether they undergo observation only or are treated with bilateral mastectomy, have an excellent prognosis. Recent data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial show that tamoxifen given for 5 years is associated with an approximately 46% reduction (hazard ratio, 0.54; 95% CI, 0.27–1.02) in the risk of developing invasive breast cancer among women with LCIS.[37,38] Results from the NSABP Study of Tamoxifen and Raloxifene (STAR) trial have shown raloxifene to be as effective as tamoxifen in reducing the risk of invasive cancer in postmenopausal patients with LCIS.[39] Therefore, the use of tamoxifen in premenopausal women, or tamoxifen or raloxifene in postmenopausal women, should be considered as a risk reduction strategy in women with LCIS who are followed up with observation (category 1). Risk reduction recommendations are provided in the NCCN Guidelines for Breast Cancer Risk Reduction (in this issue and at www.NCCN.org).

Follow-up of patients with LCIS includes interval history and physical examinations every 6 to 12 months. Annual diagnostic mammography is recommended in patients being followed up with clinical observation. Patients receiving tamoxifen or raloxifene therapy should be monitored as described in the NCCN Guidelines for Breast Cancer Risk Reduction (in this issue and at www.NCCN.org).

Ductal Carcinoma In Situ: The recommended workup and staging of DCIS includes history and physical examination; bilateral diagnostic mammography; pathology review; and tumor ER determination (see page 1185). Genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer as defined by the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian (available at www.NCCN.org).

Patients with DCIS and evidence of widespread disease (i.e., disease in ≥ 2 quadrants) on mammography or other imaging, physical examination, or biopsy require a total mastectomy without lymph node dissection. For most patients with more limited disease in whom negative margins are achieved with the initial excision or with reexcision, breast-conserving therapy or total mastectomy are appropriate treatment options. Although mastectomy provides maximum local control, its long-term, cause-specific survival seems to be equivalent to that for excision and whole-breast irradiation.[40–42] Women treated with mastectomy are appropriate candidates for breast reconstruction (see page BINV-G, available online, in these guidelines, at www.NCCN.org). Contraindications to breast-conserving therapy with radiation therapy are listed in the algorithm (see page BINV-F, available online, in these guidelines, at www.NCCN.org).

Prospective randomized trials have shown that the addition of whole-breast irradiation to a margin-free excision of pure DCIS decreases the rate of in-breast disease recurrence, but does not affect overall survival[41–45] or distant metastasis-free survival.[46] Whole-breast irradiation after breast-conserving surgery reduces the relative risk of a local failure by approximately one half. The use of a radiation boost (by photons, brachytherapy, or electron beam) to the tumor bed is recommended to maximize local control, especially in patients aged 50 years or younger.

Retrospective evidence suggests that selected patients who have undergone excision alone without breast irradiation have a low risk for in-breast recurrence.[47–50] For example, in a retrospective review, 10-year disease-free survival rates of 186 patients with DCIS treated with breast-conserving surgery alone were 94% for patients with low-risk DCIS and 83% for patients with both intermediate- and high-risk DCIS.[49] In another retrospective study of 215 patients with DCIS treated with breast-conserving

therapy without radiation therapy, endocrine therapy, or chemotherapy, the recurrence rate over 8 years was 0%, 21.5%, and 32.1% in patients with low-, intermediate-, or high-risk DCIS, respectively.[50]

A multi-institutional nonrandomized prospective study of selected patients with low-risk DCIS treated without radiation also provides some support for the use of excision without radiation in the treatment of DCIS.[51,52] At a median follow-up of 6.2 years, the 5-year risk of ipsilateral breast recurrence was 6.1% (95% CI, 4.1%–8.2%) in the subset of patients with low-/intermediate-grade DCIS and median tumor size of 6 mm. However, the 5-year rate of local ipsilateral recurrence observed in the group of patients with high-grade DCIS (median tumor size, 5 mm) was considerably higher (15.3%; 95% CI, 8.2%–22.5%) at a median follow-up of 6.7 years. Margin widths were 5 mm or larger in 69.2% and 82.9% of patients in the low-/intermediate-risk and high-risk arms, respectively, with margin widths of 10 mm or larger or no tumor on reexcision observed in 48.5% and 53.3% of patients in the respective groups. Although an acceptably low ipsilateral recurrence rate was observed in the low-/intermediate-grade arm of the study at 5 years, the 7-year ipsilateral recurrence rate in this group of patients was considerably higher (10.5%; 95% CI, 7.5%–13.6%), suggesting that these events may be delayed but not prevented in this population. Ipsilateral breast recurrences were approximately equally divided between invasive breast cancer and DCIS in the low-/intermediate-risk group, but only about one third of patients with an in-breast recurrence in the high-risk group had invasive disease.

Many factors, including patient age, tumor size, tumor grade, and margin width, impact recurrence risk. The definition of a negative margin has not been firmly established for DCIS. A consensus seems to exist that margins greater than 10 mm are adequate and margins less than 1 mm are inadequate, but no uniform consensus exists for margin status between these values. Results from a retrospective study of 445 patients with pure DCIS treated with excision alone indicated that margin width was the most important independent predictor of local recurrence, although the trend for decreasing local recurrence risk with increasing margin width was most apparent with margins less than 1 mm and greater than or equal to 6 mm.[53]

In a recent meta-analysis of 4660 patients with DCIS treated with breast-conserving surgery and radiation, a surgical margin of less than 2 mm was associated with increased rates of ipsilateral breast tumor recurrence compared with margins of 2 mm, although no significant differences were observed when margins of greater than 2 but less than 5 mm or greater than 5 mm were compared with margins of 2 mm.[54] The results of this study suggest that wide margins (≥ 2 mm), which can compromise cosmetic outcome, do not provide additional benefit for patients with DCIS who undergo radiation therapy after breast-conserving therapy. Further complicating the issue of margin width is the impact of the fibroglandular boundary, the pectoral fascia and the superficial skin where narrower tumor-free margins may provide adequate local control. Finally, because the choice of local treatment does not impact disease-related survival, the individual patient's acceptance of the potential increased risk for local recurrence must be considered.

Axillary dissection is not recommended for patients with pure DCIS, and axillary nodal involvement in DCIS is rare.[55] However, a small proportion of women with apparent pure DCIS on initial biopsy will be found to have invasive breast cancer at the definitive surgical procedure, and thus ultimately require axillary lymph node staging. In patients with apparent pure DCIS to be treated with mastectomy or with excision in an anatomic location (e.g., tail of the breast), which could compromise the performance of a future sentinel lymph node procedure, a sentinel lymph node procedure may be considered.[56–58]

The primary treatment options for women with DCIS, along with their respective categories of evidence and consensus, are:

- Lumpectomy plus radiation (category 1)
- Total mastectomy, with or without reconstruction (category 2A)
- Lumpectomy alone followed by clinical observation (category 2B)

No evidence shows that survival differs among the 3 treatment options. Decreased rates of local recurrence after lumpectomy have been observed in randomized trials with the addition of whole-breast radiation (category 1). Although randomized trials evaluating the effectiveness of total mastectomy in DCIS have not been performed, mastectomy is a highly effective strategy for decreasing the risk of local recurrence (category 2A). The option of lumpec-

tomy alone should be considered only when the patient and physician view the individual risks as "low" (category 2B).

An analysis of specimen margins and radiographs should be performed to ensure that all mammographically detectable DCIS has been excised. In addition, a postexcision mammogram should be considered when appropriate (e.g., the mass and/or microcalcifications are not clearly within the specimen).[59] Clips are used by some NCCN Member Institutions to demarcate the biopsy area, because DCIS may be clinically occult and further surgery may be required, pending the margin status review by pathology.

DCIS falls between atypical ductal hyperplasia and invasive ductal carcinoma within the spectrum of breast proliferative abnormalities. The NSABP Breast Cancer Prevention Trial showed a 75% reduction in the occurrence of invasive breast cancer in patients with atypical ductal hyperplasia treated with tamoxifen.[37,38] These data also showed that tamoxifen substantially reduced the risk for developing benign breast disease.[60] The Early Breast Cancer Trialists' overview analysis showed that, with 5 years of tamoxifen therapy, women with ER-positive or receptor-unknown invasive tumors had a 39% reduction in the annual odds of recurrence of invasive breast cancer.[2]

Similarly, the NSABP B-24 trial found a benefit from tamoxifen for women with DCIS after treatment with breast conservation surgery and radiation therapy. In that study, women with DCIS who were treated with breast-conserving therapy were randomized to receive placebo or tamoxifen. The women treated with tamoxifen had a 5% absolute reduction in recurrence risk and a 37% reduction in relative risk of recurrence. The women receiving tamoxifen had an 8.2% total incidence of breast cancer (4.1% invasive and 4.2% noninvasive) compared with a 13.4% incidence of breast cancer (7.2% invasive and 6.2% noninvasive) in the placebo-treated women at a median follow-up of 74 months.[61] The cumulative incidence of invasive breast cancer at 5 years in the ipsilateral breast was 4.2% and 2.1% in women receiving placebo and tamoxifen, respectively, and in the contralateral breast was 2.3% and 1.8% in the placebo and tamoxifen groups, respectively. A retrospective analysis of ER expression in NSABP B-24 suggests that increased levels of ER expression predict for tamoxifen benefit in terms of reduction of risk for the development of both ipsilateral and contralateral breast cancer after breast-conserving therapy.[62]

Tamoxifen treatment, therefore, may be considered as a strategy to reduce the risk of ipsilateral breast cancer recurrence in women with DCIS treated with breast-conserving therapy, especially in those with ER-positive DCIS (category 1 for those undergoing breast-conserving surgery plus radiation therapy; category 2A for those undergoing excision alone). Tamoxifen may also be considered as a risk reduction therapy to decrease risk of contralateral breast cancer in women with DCIS who have undergone a lumpectomy (with or without radiation) and in women with DCIS treated with mastectomy (category 2B).

Follow-up of women with DCIS includes interval history and physical examination every 6 to 12 months for 5 years and then annually, and yearly diagnostic mammography. In patients undergoing breast-conserving therapy, the first follow-up mammogram should be performed 6 to 12 months after the completion of breast-conserving radiation therapy (category 2B). Patients receiving tamoxifen should be monitored as described in the NCCN Guidelines for Breast Cancer Risk Reduction (in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Most recurrences of DCIS are in-breast recurrences after breast-conserving therapy, and most recurrences occur close to the site of prior disease. In women for whom the initial DCIS was treated with excision alone, the treatment decision-making for a recurrence of DCIS is similar to that followed previously. In women for whom the initial DCIS was treated with breast-conserving surgery plus radiation therapy, mastectomy is usually necessary after a recurrence of DCIS. Local recurrences after mastectomy for DCIS should be treated with wide local excision with consideration of chest wall irradiation.

Overall, approximately half of the local recurrences after initial treatment for a pure DCIS are again DCIS, and the others are invasive cancer. Women with local recurrences that are invasive should undergo systemic treatment as appropriate for a newly diagnosed invasive breast cancer.

Special Situations

Paget's Disease: Paget's disease of the breast is a rare manifestation of breast cancer characterized by neoplastic cells in the epidermis of the nipple areolar

complex.[359] It most commonly presents with eczema of the areola, bleeding, ulceration, and itching of the nipple. The diagnosis is often delayed because of the rare nature of the condition and confusion with other dermatologic conditions. An associated cancer is present elsewhere in the breast in up to 80% to 90% of cases.[360–362] The associated cancers are not necessarily located adjacent to the nipple areolar complex, and may be either DCIS or invasive cancer.

Women with clinical signs suggesting Paget's disease require a complete history, physical examination, and diagnostic breast imaging (see page 1190). Any breast lesion identified on imaging or examination should be evaluated according to the NCCN Guidelines for Breast Cancer Screening and Diagnosis (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). The skin of the nipple areolar complex should undergo surgical biopsy that includes the full thickness of the epidermis and at least a portion of any clinically involved nipple areola complex. When biopsy of the nipple areola complex is positive for Paget's disease, breast MRI is recommended to define the extent of disease and identify additional disease (see page 1191 and online, in these guidelines, at www.NCCN.org [BINV-B]).[362,363]

No category 1 data specifically address local management of Paget's disease. Systemic therapy is based on the stage and biologic characteristics of any underlying cancer, and is supported by evidence cited in the relevant stage-specific breast cancer treatment guidelines.

Management of Paget's disease has traditionally been total mastectomy with axillary dissection. Total mastectomy remains a reasonable option for patients regardless of the absence or presence of an associated breast cancer.[360] Recent data show that satisfactory local control may be achieved with breast-conserving surgery that includes excision with negative margins of any underlying breast cancer, along with resection of the nipple areolar complex followed by whole-breast radiation therapy.[364–369] The risk for ipsilateral breast cancer recurrence after breast-conserving nipple areola complex resection and radiation therapy with or without an associated cancer is similar to that associated with breast-conserving surgery and radiation therapy for the typical invasive or in situ cancer.

For Paget's disease without an associated cancer (i.e., no palpable mass or imaging abnormality), breast-conserving surgery should consist of removal of the entire nipple areola complex with a negative margin of underlying breast tissue. When an associated cancer is present elsewhere in the breast, the surgery should include removal of the nipple areolar complex with a negative margin, and removal of the peripheral cancer using a standard breast-conserving technique to achieve a negative margin. It is not necessary to remove the nipple areolar complex and the peripheral cancer in continuity in a single surgical specimen or through a single incision. Mastectomy also remains an appropriate treatment option (see page 1191).

Axillary lymph node staging is not necessary when breast-conserving therapy is used to treat Paget's disease with underlying DCIS in the absence of evidence of invasive cancer based on clinical examination, imaging evaluation, and full-thickness skin biopsy of the involved nipple areola complex. In the presence of an underlying invasive breast cancer treated with breast-conserving surgery, axillary surgery should be performed according to the Surgical Axillary Staging guideline (available online, in these guidelines, at www.NCCN.org [BINV-C]). In cases treated with total mastectomy, axillary staging is recommended for patients with invasive disease and should also be considered for patients with underlying DCIS without evidence of invasive disease, because the final pathology may reveal an invasive cancer in the mastectomy specimen, and the mastectomy precludes subsequent sentinel node biopsy. Two retrospective studies have provided evidence for a high degree of accuracy in the identification of the sentinel nodes in patients with Paget's disease.[370,371]

Patients treated with breast conservation should undergo whole-breast radiation. Extended-field radiation to regional lymph nodes should be used in cases of an associated invasive breast cancer with involved lymph nodes as for any breast cancer, as described online, in these guidelines, at www.NCCN.org (BINV-2). A radiation boost should be considered to the site of the resected nipple areolar complex and any associated resected cancer site, if applicable.

Women with an associated invasive cancer have substantial risk of developing metastases. Adjuvant systemic therapy should be administered according to the stage of the cancer. Women with Paget's disease treated with breast conservation and without an associated cancer, or those with associated DCIS,

should consider tamoxifen for risk reduction. Those with an associated invasive cancer should undergo adjuvant systemic therapy based on the stage and hormone receptor status, as outlined online, in these guidelines, at www.NCCN.org [BINV-4 to BINV-9].

Phyllodes Tumors of the Breast: Phyllodes tumors of the breast (also known as *phylloides tumors* and *cystosarcoma phyllodes*) are rare tumors consisting of both stromal and epithelial elements.[372] Phyllodes tumors exist in benign, borderline, and malignant subtypes, although no uniform agreement exists on the criteria for assigning subtype or for predicting biologic behavior.[373] Subtype of phyllodes tumor seems to be less important in predicting risk of recurrence than does the margin of tumor-free resection achieved through surgical treatment. Diagnosis of phyllodes tumors before excisional biopsy/lumpectomy is uncommon. Phyllodes tumors occur in an older age distribution than fibroadenoma, a younger age distribution than the invasive ductal and lobular cancers, and with a mean age in the 40s.[374] Phyllodes tumors often enlarge rapidly and are usually painless. Phyllodes tumors often appear on ultrasound and mammography as fibroadenomas, and fine needle aspiration (FNA) cytology and even core needle biopsy are inadequate to reliably distinguish phyllodes tumors from fibroadenoma.[374] Thus, in the setting of a large or rapidly enlarging clinical fibroadenoma, excisional biopsy should be considered to pathologically exclude a phyllodes tumor. Patients with the Li-Fraumeni syndrome (germline *p53* mutation, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian; available at www.NCCN.org) have an increased risk of phyllodes tumors.[375] Recurrences of phyllodes tumors are most commonly seen locally. Most distant recurrences occur in the lung, and may be solid nodules or thin-walled cavities.

Treatment of phyllodes tumors (including benign, borderline, and malignant subtypes) is with local surgical excision with tumor-free margins of 1 cm or greater. Lumpectomy or partial mastectomy is the preferred surgical therapy. Total mastectomy is necessary only if negative margins cannot be obtained with lumpectomy or partial mastectomy[376] (see page 1188). Because phyllodes tumors rarely metastasize to the axillary lymph nodes, surgical axillary staging or axillary lymph node dissection is not necessary unless the lymph nodes are pathologic on clinical examination.[377] In patients who experience a local recurrence, resection of the recurrence with wide tumor-free surgical margins should be performed (see page 1189). Some members of the panel recommend local radiation therapy of the remaining breast or chest wall after resection of a local recurrence, but this recommendation is controversial (category 2B).[378]

Although the epithelial component of most phyllodes tumors contains ER (58%) and/or PR (75%),[379] endocrine therapy has no proven role in the treatment of phyllodes tumors. Similarly, no evidence shows that adjuvant cytotoxic chemotherapy reduces the rate of recurrences or death. In the rare patient who experiences a systemic recurrence (usually in the lung), treatment should be as recommended as per the NCCN Guidelines for Soft Tissue Sarcoma (available at www.NCCN.org).

Breast Cancer During Pregnancy: Breast cancer occurring concurrent with pregnancy is an infrequent clinical event. In a California registry study, 1.3 breast cancers were diagnosed per 10,000 live births.[380] Unfortunately, breast cancer during pregnancy is most often axillary lymph node–positive and has larger primary tumor size. Histologically, the tumors are poorly differentiated, are more frequently ER- and PR-negative, and approximately 30% are HER2-positive.[381,382] The diagnosis is often delayed because neither the patient nor the physician suspects malignancy.

Evaluation of the pregnant patient with suspected breast cancer should include a physical examination with particular attention to the breast and regional lymph nodes. Mammogram of the breast with shielding can be performed safely and the accuracy is reported to be greater than 80%.[383] Ultrasound of the breast and regional lymph nodes can be used to assess the extent of disease and also to guide biopsy. Ultrasound has been reported to be abnormal in up to 100% of breast cancers occurring during pregnancy.[383] Biopsies for cytologic evaluation of a suspicious breast mass may be done with an FNA of the breast and suspicious lymph nodes. However, the preferred technique is core needle biopsy because it provides tissue for histologic confirmation of invasive disease and adequate tissue for hormone receptor and HER2 analyses.

Staging assessment of the pregnant patient with breast cancer may be guided by clinical disease stage. For clinically node-negative T1–T2 tumors, a chest radiograph (with shielding), liver and renal function

assessment, and complete blood cell count with differential are appropriate. In addition to these studies, an ultrasound of the liver and consideration of a screening MRI of the thoracic and lumbar spine without contrast may be used in patients who have clinically node-positive or T3 breast lesions. Documenting the presence of metastases may alter the treatment plan and influence the patient's decision regarding maintenance of the pregnancy.

Assessment of the pregnancy should include a maternal fetal medicine consultation and review of antecedent maternal risks, such as hypertension, diabetes, and complications with prior pregnancies. Documenting fetal growth and development and fetal age through ultrasonographic assessment is appropriate. Estimating the delivery date will help in planning treatment with systemic chemotherapy. In addition, maternal fetal medicine consultation should include counseling regarding maintaining or terminating pregnancy. Counseling of the pregnant patient with breast cancer should include a review of the treatment options, which include mastectomy or breast-conserving surgery and the use of systemic therapy. The most common surgical procedure has been modified radical mastectomy. However, Kuerer et al.[384] showed that breast-conserving surgery is possible if radiation therapy can be delayed to the postpartum period, and breast-conserving therapy during pregnancy does not seem to have a negative impact on survival.[384,385] When surgery is performed at 25 weeks gestation or later, obstetrical and prenatal specialists must be on site and immediately available in the event of precipitous delivery of a viable fetus.

Although a limited number of isolated case reports and small retrospective studies have evaluated the use of sentinel lymph node biopsy in pregnant patients,[386,387] the sensitivity and specificity of the procedure has not been established in this setting. Therefore, data are insufficient on which to base recommendations for its use in the pregnant woman. Decisions related to use of sentinel lymph node biopsy in pregnancy should be individualized. A recent review of the relative and absolute contraindications to sentinel node biopsy concluded that this procedure should not be offered to pregnant women under 30 weeks gestation.[388] Limited data exist on use of radioactive tracer (e.g., technetium 99m sulfur colloid), with only case reports and estimations of fetal radiation dose.[389–391] Isosulfan blue or methylene blue dye for sentinel node biopsy procedures is discouraged during pregnancy.

The indications for systemic chemotherapy to treat breast cancer are the same in the pregnant patient as in the nonpregnant patient, although chemotherapy should not be administered at any point during the first trimester of pregnancy. The greatest experience in pregnancy has been with anthracycline and alkylating chemotherapy agents.[392,393] Collected data of chemotherapy exposure in utero indicate that the greatest risk for fetal malformation occurs in the first trimester.[394,395] The risk for fetal malformation in the second and third trimester is approximately 1.3%, which is not different from that for fetuses not exposed to chemotherapy during pregnancy. If systemic therapy is initiated, fetal monitoring before each chemotherapy cycle is appropriate. Chemotherapy during pregnancy should not be given after week 35 of pregnancy or within 3 weeks of planned delivery to avoid the potential for hematologic complications at delivery. Recent data from a single institution prospective study indicate that FAC chemotherapy (5-FU 500 mg/m^2 intravenously day 1 and 4, doxorubicin 50 mg/m^2 by intravenous infusion over 72 hours, and cyclophosphamide 500 mg/m^2 intravenously day 1) may be given with relative safety during the second and third trimesters of pregnancy.[393] Ondansetron, lorazepam, and dexamethasone can be used as part of the prechemotherapy antiemetic regimen. In their study, Gwyn and Theriault[382] reported that the median gestational age at delivery was 38 weeks, more than 50% of the patients had vaginal delivery, and no fetal deaths occurred. An update of this experience reported on 57 women treated with FAC in the adjuvant or neoadjuvant setting, with 57 live births. In a survey of parents/guardians that reported on the health of 40 children, 1 child had Down's syndrome and 2 had congenital abnormalities (club foot and congenital bilateral ureteral reflux). The children are reported to be healthy and progressing well in school.[393,396]

Ondansetron, lorazepam, and dexamethasone can be used as part of the prechemotherapy antiemetic regimen.

Because limited data are available on the use of taxanes during pregnancy, they are not recommended during pregnancy.[397–401] If taxane use is clinically indicated, it may be used in the postdelivery setting. Preferred chemotherapy choices are the doxorubi-

cin-based regimens that have already been evaluated in pregnant patients.

Only case reports exist of trastuzumab use during pregnancy.[402–409] Most of these case reports indicated oligo- or anhydramnios with administration of trastuzumab; fetal renal failure occurred in one case. If trastuzumab is otherwise indicated, it should be administered in the postpartum period; the panel recommends against its use during pregnancy.

A single case report of first-trimester exposure to lapatinib during treatment for breast cancer reported an uncomplicated delivery of a healthy female neonate.[410]

Endocrine and radiation therapy are contraindicated during pregnancy. If indicated, they should not be initiated until the postpartum period.

Communication between the oncologist and maternal fetal medicine specialist is essential at every visit and treatment decision point for the patient (see page 1192).

Axillary Breast Cancer: Axillary metastasis from an occult breast cancer represents 3% to 5% of breast cancers. Evidence supporting recommendations for managing these patients comes from a limited number of retrospective studies involving small numbers of patients[430–432] (see also references therein). Although treatment of women with axillary metastases from an unknown primary tumor has typically involved mastectomy and axillary nodal dissection, some of these patients have also been successfully treated with axillary nodal dissection followed by radiation therapy.[431,432]

Some evidence indicates that MRI of the breast can facilitate the identification of occult breast cancer, and can help select patients most likely to benefit from mastectomy. For example, in a study of 40 patients with biopsy-proven breast cancer in the axilla and a negative or indeterminate mammogram, MRI identified the primary breast lesion in 70%.[432] In addition, among the 7 patients with a negative MRI who subsequently underwent axillary lymph node dissection and radiation therapy to the whole breast, no evidence of local recurrence was evident at a median follow-up of 19 months.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Occult Primary (Cancer of Unknown Primary) provide guidance on the diagnosis and initial workup of patients with a suspicious axillary mass in the absence of any signs of a primary tumor (to view the most recent version, visit the NCCN Web site at www.NCCN.org). (Notably, a small subset of these patients may have a primary cancer in the axillary tail of the breast.) These guidelines also provide recommendations for additional workup, including chest and abdominal CT, to evaluate for evidence of distant metastases in patients diagnosed with adenocarcinoma (or carcinoma not otherwise specified) of the axillary nodes without evidence of a primary breast lesion. In particular, breast MRI and ultrasound are recommended. Axillary ultrasound should also be performed.

Patients with MRI-positive disease should undergo further evaluation with ultrasound or MRI-guided biopsy and undergo treatment according to the clinical stage of the breast cancer. Treatment recommendations for those with MRI-negative disease are based on nodal status. For patients with T0, N1, M0 disease, options include either mastectomy plus axillary nodal dissection or axillary nodal dissection plus whole-breast irradiation with or without nodal irradiation (see page BINV-H, available online, in these guidelines, at www.NCCN.org). Systemic chemotherapy, endocrine therapy, or trastuzumab is given according to the recommendations for stage II or III disease (see page BINV-4, available online, in these guidelines, at www.NCCN.org). Neoadjuvant chemotherapy, trastuzumab, and endocrine therapy should be considered for patients with T0, N2–N3, M0 disease followed by axillary nodal dissection and mastectomy, as for patients with locally advanced disease (see pages BINV-4 to BINV-14, at www.NCCN.org).

Summary

The therapeutic options for patients with noninvasive or invasive breast cancer are complex and varied. In many situations, the patient and physician have the responsibility to jointly explore and select the most appropriate option from among the available alternatives.

With few exceptions, the evaluation, treatment, and follow-up recommendations in these guidelines are based on the results of past and present clinical trials. However, no single clinical situation exists in which the treatment of breast cancer has been optimized with respect to either maximizing cure or minimizing toxicity and disfigurement. Therefore, patient/physician participation in prospective clinical trials allows patients to not only receive state-

of-the-art cancer treatment but also contribute to improving the treatment of future patients.

Guidelines Online

Information on invasive and inflammatory breast cancer can be found in the full breast cancer guidelines, available online at www.NCCN.org.

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