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Invasive Breast Cancer

Clinical Practice Guidelines in Oncology

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Overview

These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer are the work of the members of the NCCN Breast Cancer Panel. 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 NCCN Guidelines, patient participation in prospective clinical trials is the preferred option of treatment for all stages of breast cancer. The full breast cancer guidelines are not printed in this issue of *JNCCN*, but can be accessed online at

NCCN Clinical Practice Guidelines in Oncology for Invasive Breast Cancer

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, breast cancer, chemotherapy, breast-conserving therapy, adjuvant therapy, mastectomy, endocrine therapy, radiation, therapy, lobular carcinoma in situ, ductal carcinoma in situ *(JNCCN* 2011;9:136–222)

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 Invasive Breast Cancer

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 Invasive Breast Cancer panel members can be found on page 222. (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.

www.NCCN.org.

The American Cancer Society estimated that 209,060 new cases of invasive breast cancer were diagnosed and 40,230 people died of breast cancer in the United States in 2010.[1] In addition, approximately 54,010 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 cause 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 birth, prolonged hormone replacement therapy, previous exposure to therapeutic chest wall irradiation, benign proliferative breast disease, and genetic mutations, such as of the *BRCA1/2* genes. However, except for female sex and increasing patient age, these risk factors are associated with only a 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

Text continues on p. 178

NCCN Invasive Breast Cancer Panel Members

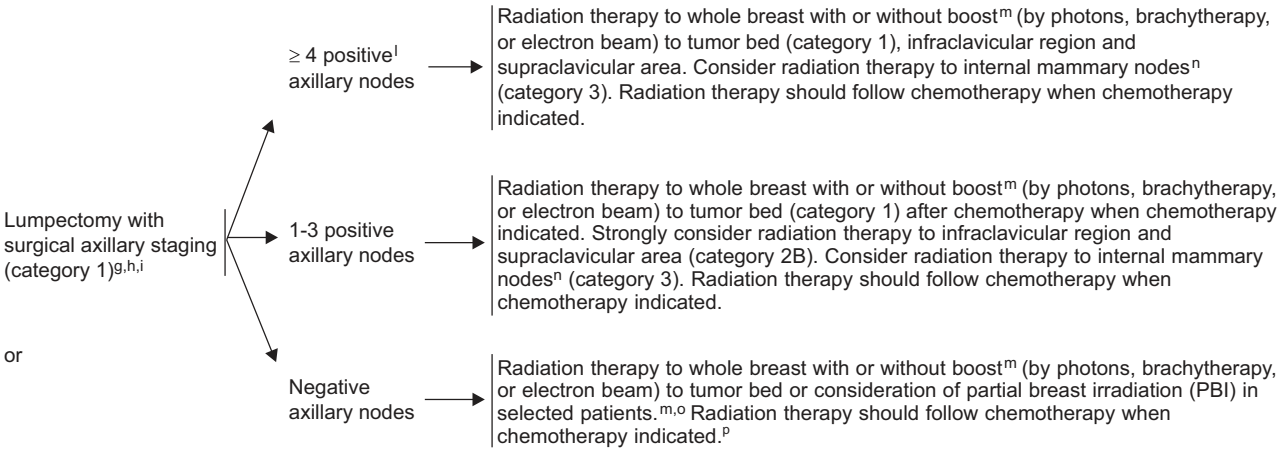
CLINICAL STAGE	WORKUP
Stage I T1,N0,M0 or Stage IIA T0,N1,M0 T1,N1,M0 T2,N0,M0 or Stage IIB T2,N1,M0 T3,N0,M0 or Stage IIIA T3,N1,M0	General workup including: • History and physical exam • CBC, platelets • Liver function tests and alkaline phosphatase • Diagnostic bilateral mammogram, ultrasound as necessary • Pathology review[a] • Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER2 status[b] • Genetic counseling if patient is high risk for hereditary breast cancer[c] Optional additional studies for breast imaging: • Breast MRI If clinical stage IIIA (T3,N1,M0) consider: • Bone scan (category 2B) • Abdominal ± pelvis CT or US or MRI • Chest imaging Additional studies as directed by signs or symptoms: • Bone scan indicated if localized bone pain or elevated alkaline phosphatase • Abdominal ± pelvis CT or US or MRI if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, abnormal physical examination of the abdomen or pelvis • Chest imaging (if pulmonary symptoms are present) • Optional FDG PET/CT (for T3,N1,M0; category 2B)[e] • Consider fertility counseling if indicated[f]

For the NCCN Guidelines for Inflammatory Breast Cancer, see the discussion on page 207 and the NCCN Web site at www.NCCN.org.

[a]The panel endorses the College of American Pathology Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. Available at http://www.cap.org.
[b]See Principles of HER2 Testing (page 159).
[c]See 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.
[d]See Principles of Dedicated Breast MRI Testing (page 160).
[e]PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease. FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.
[f]See Fertility and Birth Control After Adjuvant Breast Cancer Treatment (page 160).

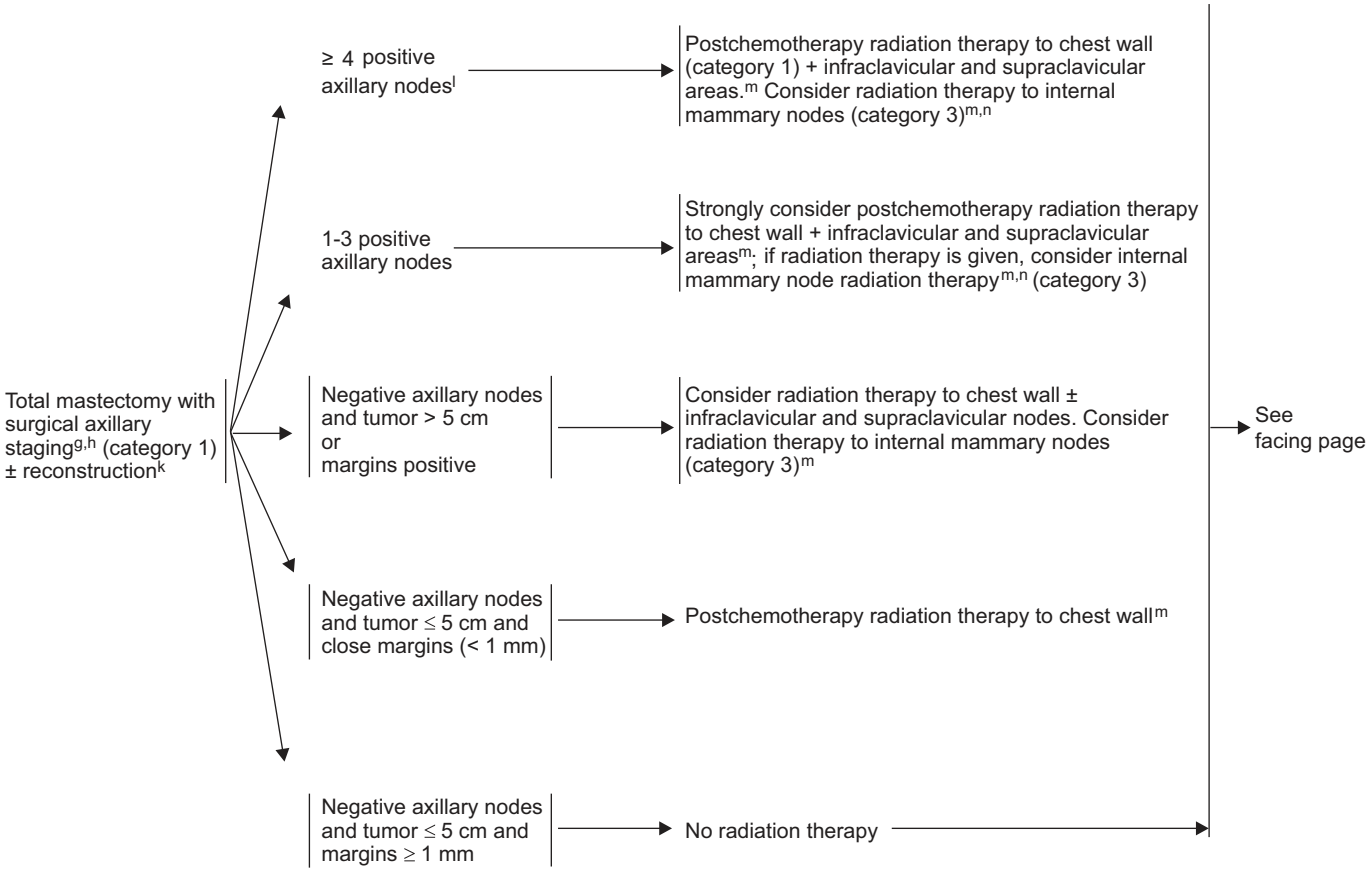
Invasive Breast Cancer Version 2:2011

LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3,N1,M0



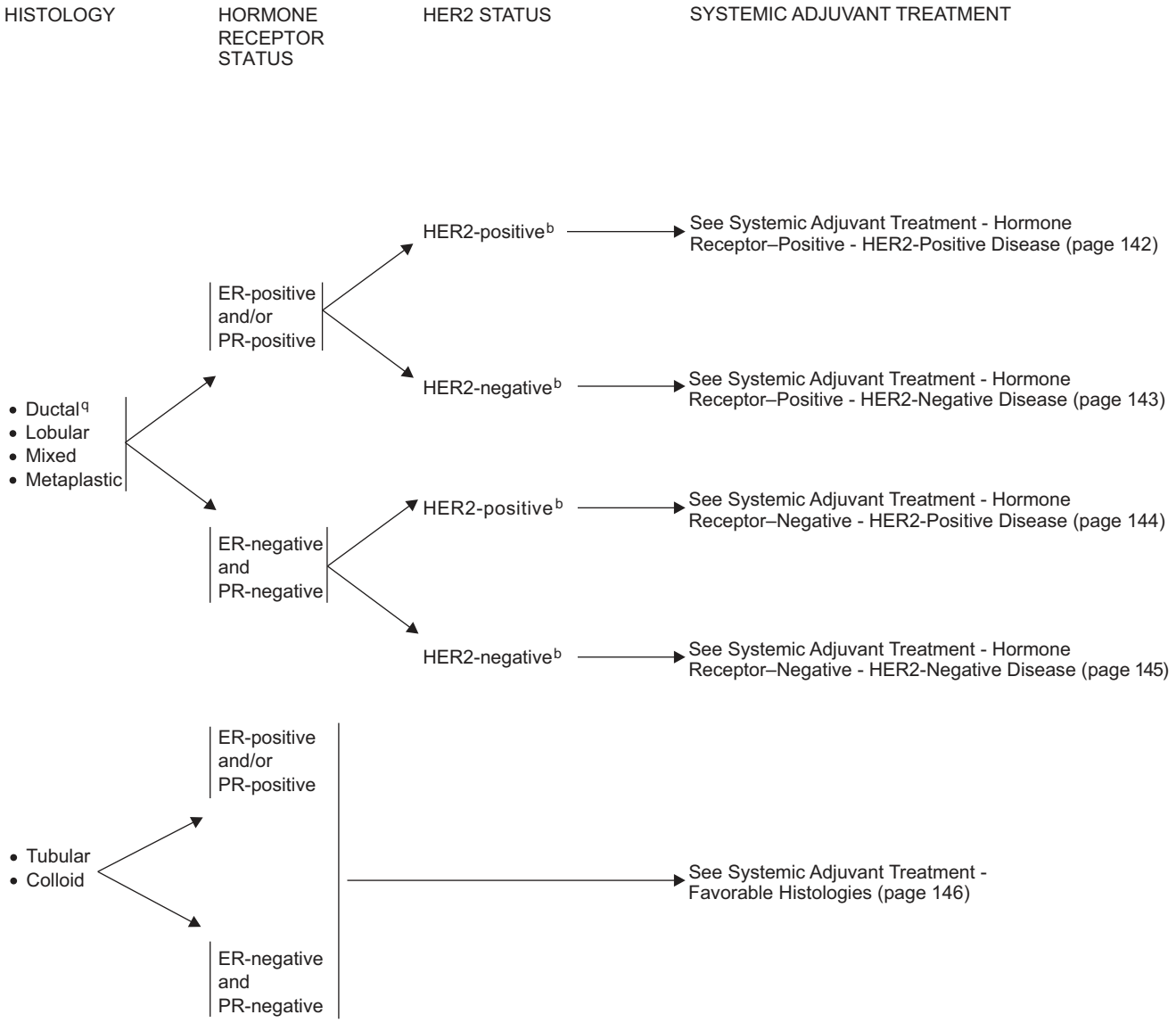
[g] See Surgical Axillary Staging (page 161).
[h] See Axillary Lymph Node Staging (page 160) and Margin Status in Infiltrating Carcinoma (page 162).
[i] See Special Considerations to Breast-Conserving Therapy (page 162).
[j] Except as outlined in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian and the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer Risk Reduction, prophylactic mastectomy of a breast contralateral to a known unilateral breast cancer is discouraged (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). When considered, the small benefits from contralateral prophylactic mastectomy for women with unilateral breast cancer must be balanced with the risk of recurrent disease from the known ipsilateral breast cancer, psychological and social issues associated with bilateral mastectomy, and the risks of contralateral mastectomy. The use of a prophylactic mastectomy contralateral to a breast treated with breast-conserving therapy is very strongly discouraged.
[k] See Principles of Breast Reconstruction Following Surgery (page 163).
[l] Consideration may be given to additional staging, including bone scan, abdominal CT/US/MRI, and chest CT (category 2B).
[m] See Principles of Radiation Therapy (page 164).
[n] Radiation therapy should be given to the internal mammary lymph nodes if they are clinically or pathologically positive, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be used whenever radiation therapy is delivered to the internal mammary lymph nodes.
[o] PBI may be administered before chemotherapy.
[p] Breast irradiation may be omitted in patients aged 70 y or older with estrogen-receptor–positive, clinically node-negative, T1 tumors who undergoadjuvant endocrine therapy (category 1).

LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3,N1,M0



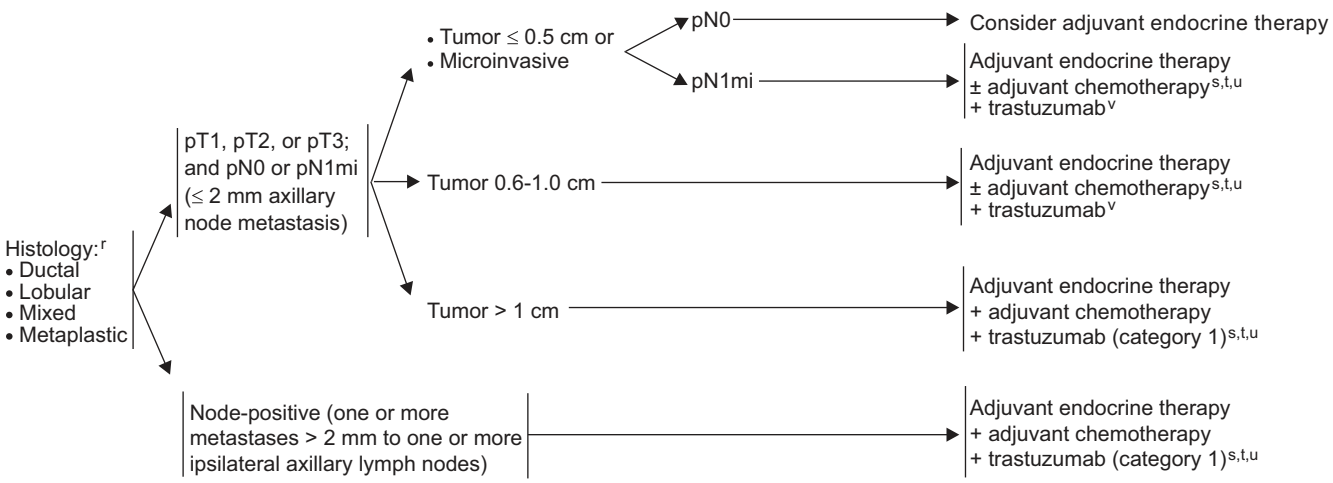
[g] See Surgical Axillary Staging (page 161).
[h] See Axillary Lymph Node Staging (page 160) and Margin Status in Infiltrating Carcinoma (page 162).
[k] See Principles of Breast Reconstruction Following Surgery (page 163).
[l] Consideration may be given to additional staging, including bone scan, abdominal CT/US/MRI, and chest CT (category 2B).
[m] See Principles of Radiation Therapy (page 164).
[n] Radiation therapy should be given to the internal mammary lymph nodes that are clinically or pathologically positive, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be used whenever radiation therapy is delivered to the internal mammary lymph nodes.

Invasive Breast Cancer Version 2:2011



[b] See Principles of HER2 Testing (page 159).
[q] This includes medullary and micropapillary subtypes.

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR–POSITIVE - HER2-POSITIVE DISEASE[b]



See Follow-Up (page 153)

See Adjuvant Endocrine Therapy (page 165) and Adjuvant Chemotherapy (pages 166-170)

[b] See Principles of HER2 Testing (page 159).

[r] Mixed lobular and ductal carcinoma and metaplastic carcinoma should be graded based on the ductal component and treated based on this grading. The metaplastic or mixed component does not alter prognosis.

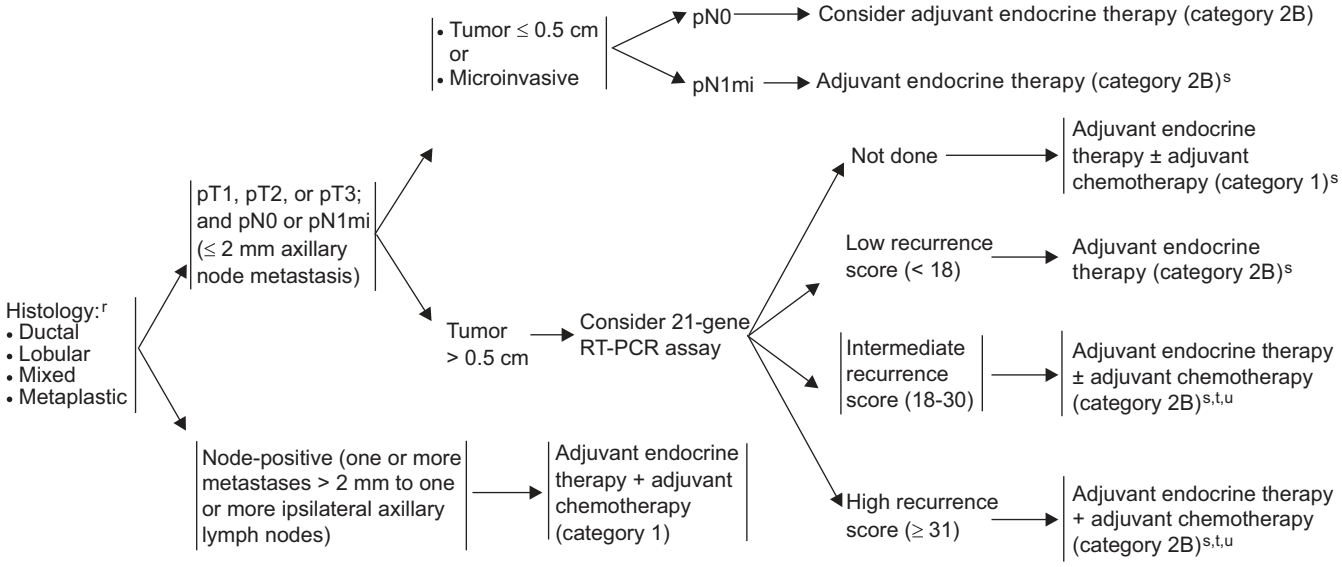
[s] Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone-receptor–positive breast cancer is similar to that achieved with CMF alone. Early evidence suggests similar benefits from ovarian suppression (i.e., luteinizing hormone-releasing hormone agonist) as from ovarian ablation. The combination of ovarian ablation/suppression plus endocrine therapy may be superior to suppression alone. The benefit of ovarian ablation/suppression in premenopausal women who have undergone adjuvant chemotherapy is uncertain.

[t] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy after chemotherapy. The benefits of chemotherapy and endocrine therapy are additive. However, the absolute benefit from chemotherapy may be small. The decision to add chemotherapy to endocrine therapy should be individualized, especially in patients with a favorable prognosis in whom the incremental benefit of chemotherapy may be smaller. Available data suggest sequential or concurrent endocrine therapy with radiation therapy is acceptable.

[u] Limited data are available to make chemotherapy recommendations for patients older than 70 y. Treatment should be individualized with consideration of comorbid conditions.

[v] The prognosis of patients with T1a and T1b tumors that are node-negative is generally favorable, even when HER2 is amplified or overexpressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision to use trastuzumab therapy in this cohort of patients must balance its known toxicities, such as cardiac toxicity, and the uncertain, absolute benefits it may have.

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR–POSITIVE - HER2-NEGATIVE DISEASE[b]



[b] See Principles of HER2 Testing (page 159).

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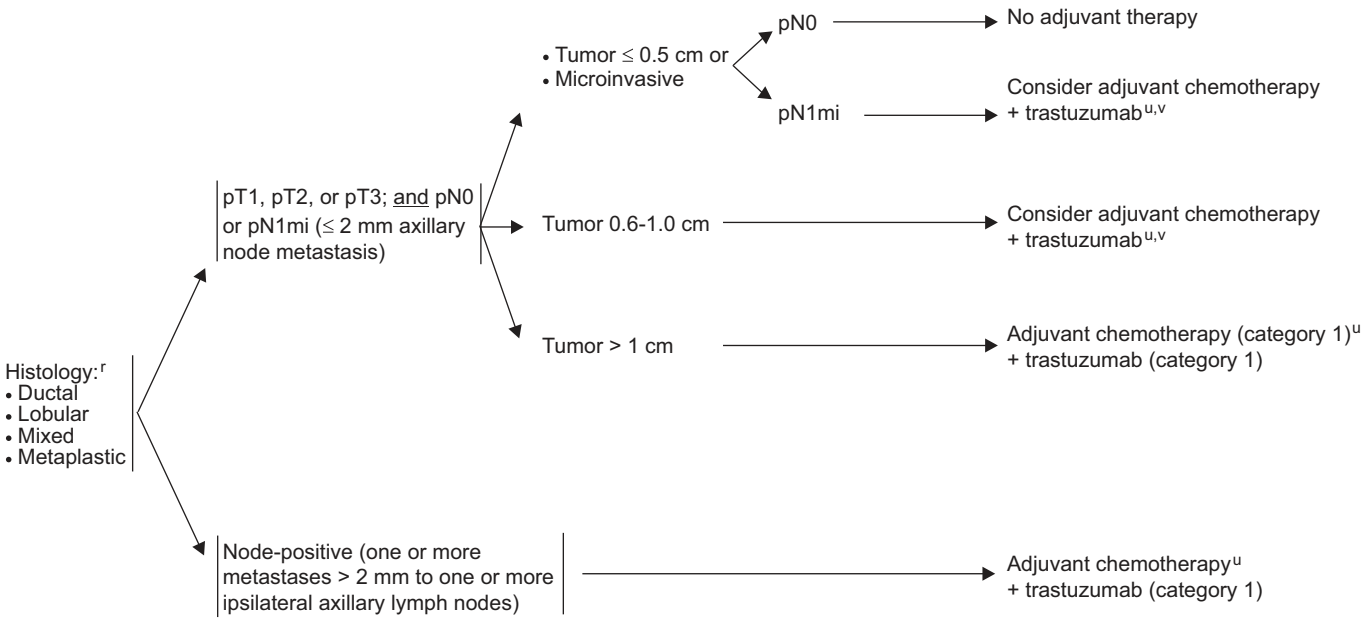
SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR–NEGATIVE - HER2-POSITIVE DISEASE[b]



See Follow-Up (page 153)

See Adjuvant Chemotherapy (pages 166-170)

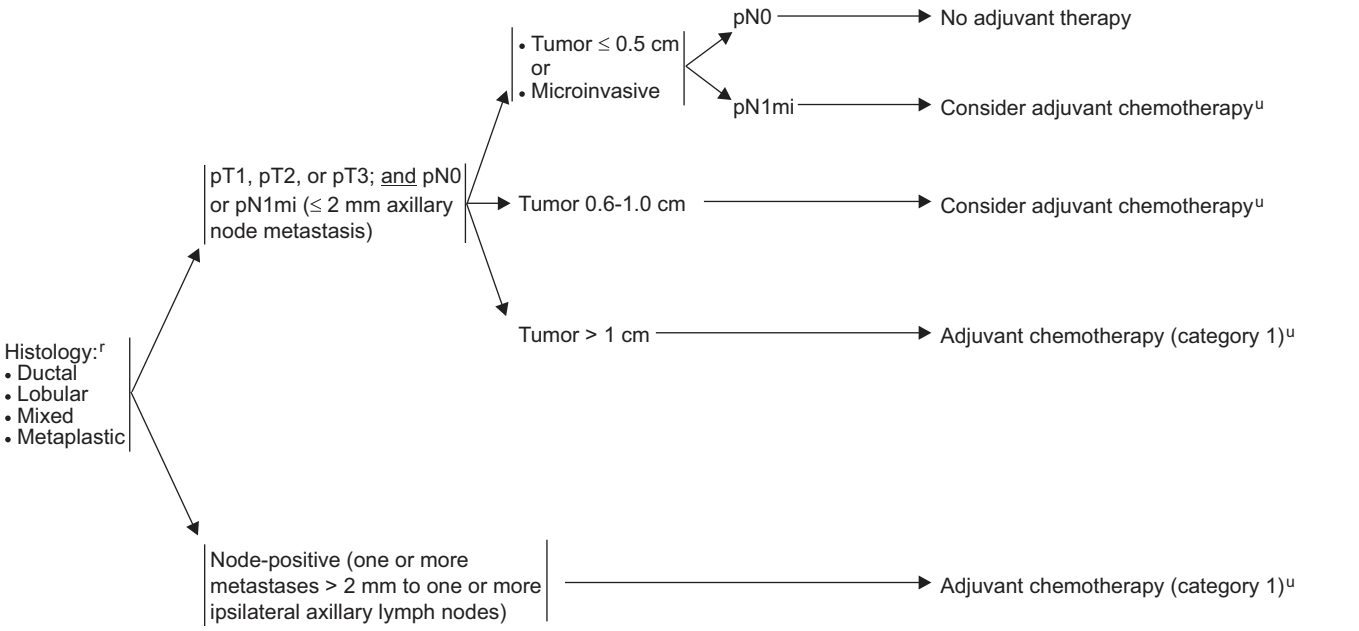
[b]See Principles of HER2 Testing (page 159).

[r]Mixed lobular and ductal carcinoma and metaplastic carcinoma should be graded based on the ductal component and treated based on this grading. The metaplastic or mixed component does not alter prognosis.

[u]Limited data are available to make chemotherapy recommendations for patients older than 70 y. Treatment should be individualized with consideration of comorbid conditions.

[v]The prognosis of patients with T1a and T1b tumors that are node-negative is generally favorable even when HER2 is amplified or overexpressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision to use trastuzumab therapy in this cohort of patients must balance its known toxicities, such as cardiac toxicity, with the uncertain, absolute benefits it may have.

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR–NEGATIVE-HER2 NEGATIVE DISEASE[b]



See Follow-Up (page 153)

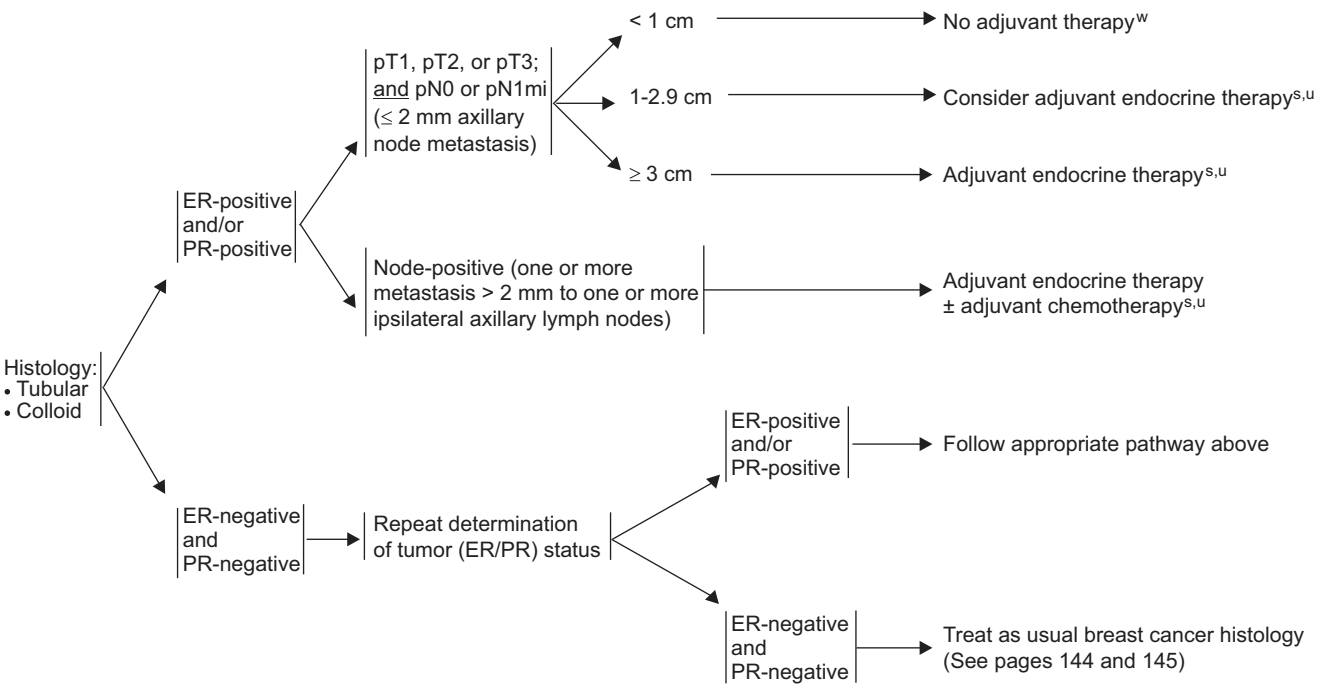
See Adjuvant Chemotherapy (pages 166-170)

[b] See Principles of HER2 Testing (page 159).

[r] Mixed lobular and ductal carcinoma and metaplastic carcinoma should be graded based on the ductal component and treated based on this grading. The metaplastic or mixed component does not alter prognosis.

[u] Limited data are available to make chemotherapy recommendations for patients older than 70 y. Treatment should be individualized with consideration of comorbid conditions.

SYSTEMIC ADJUVANT TREATMENT - FAVORABLE HISTOLOGIES



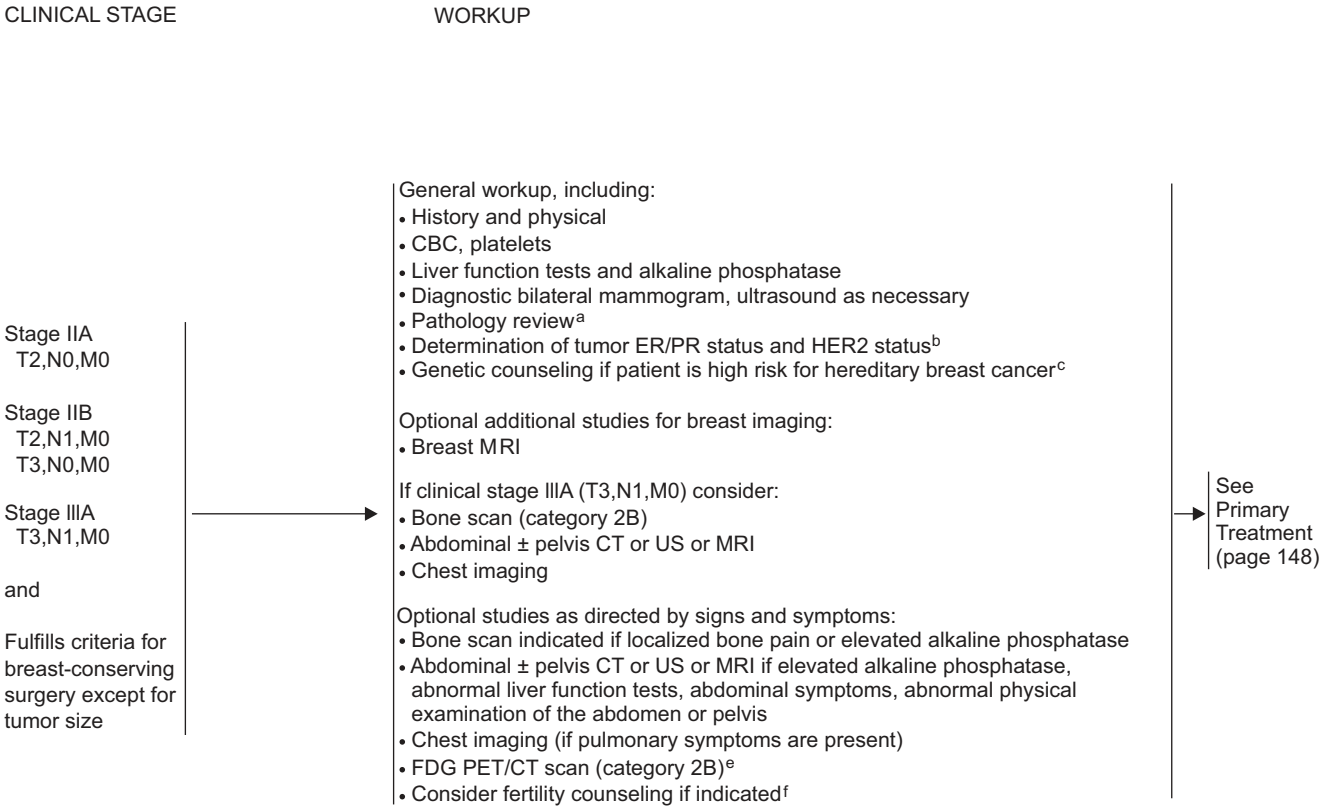
See Adjuvant Endocrine Therapy (page 165) and Adjuvant Chemotherapy (pages 166-170)

[s]Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone-receptor–positive breast cancer is similar to that achieved with CMF alone. Early evidence suggests similar benefits from ovarian suppression (i.e., luteinizing hormone-releasing hormone agonist or antagonist) as from ovarian ablation. The combination of ovarian ablation/suppression plus endocrine therapy may be superior to suppression alone. The benefit of ovarian ablation/suppression in premenopausal women who have undergone adjuvant chemotherapy is uncertain.

[u]Limited data are available to make chemotherapy recommendations for patients older than 70 y old. Treatment should be individualized with consideration of comorbid conditions.

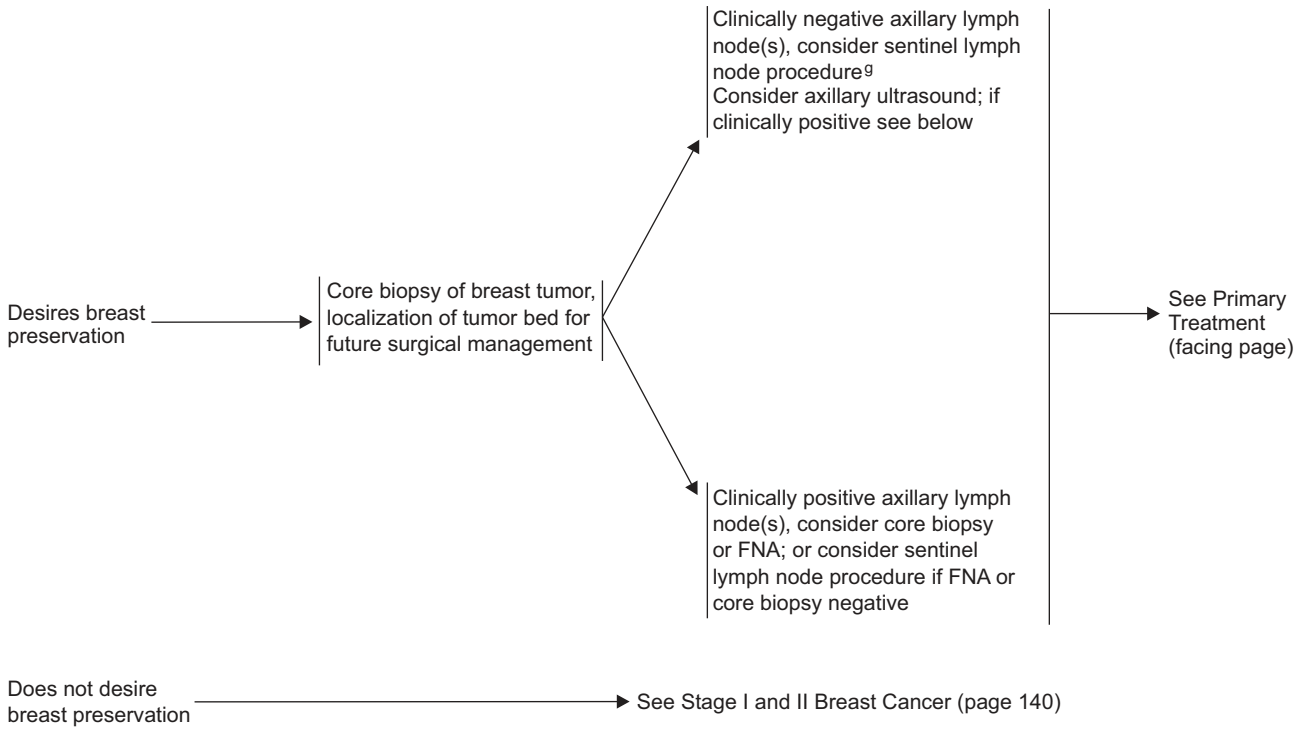
[w]If ER-positive, consider endocrine therapy for risk reduction and to diminish the small risk of disease recurrence.

Preoperative Chemotherapy Guideline



[a] The panel endorses the College of American Pathology Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. Available at http://www.cap.org.
[b] See Principles of HER2 Testing (page 159).
[c] See 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.
[d] See Principles of Dedicated Breast MRI Testing (page 160).
[e] PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease. FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.
[f] See Fertility and Birth Control After Adjuvant Breast Cancer Treatment (page 160).

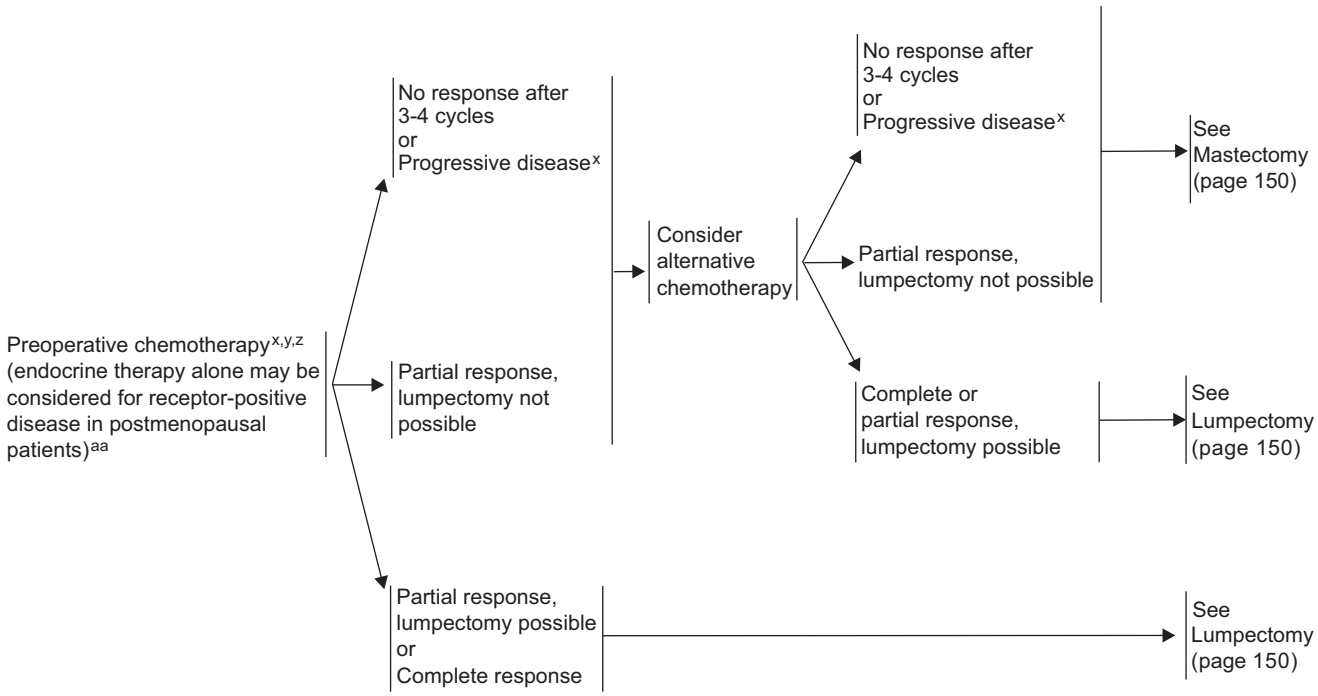
Preoperative Chemotherapy Guideline



[g] See Surgical Axillary Staging (page 161).

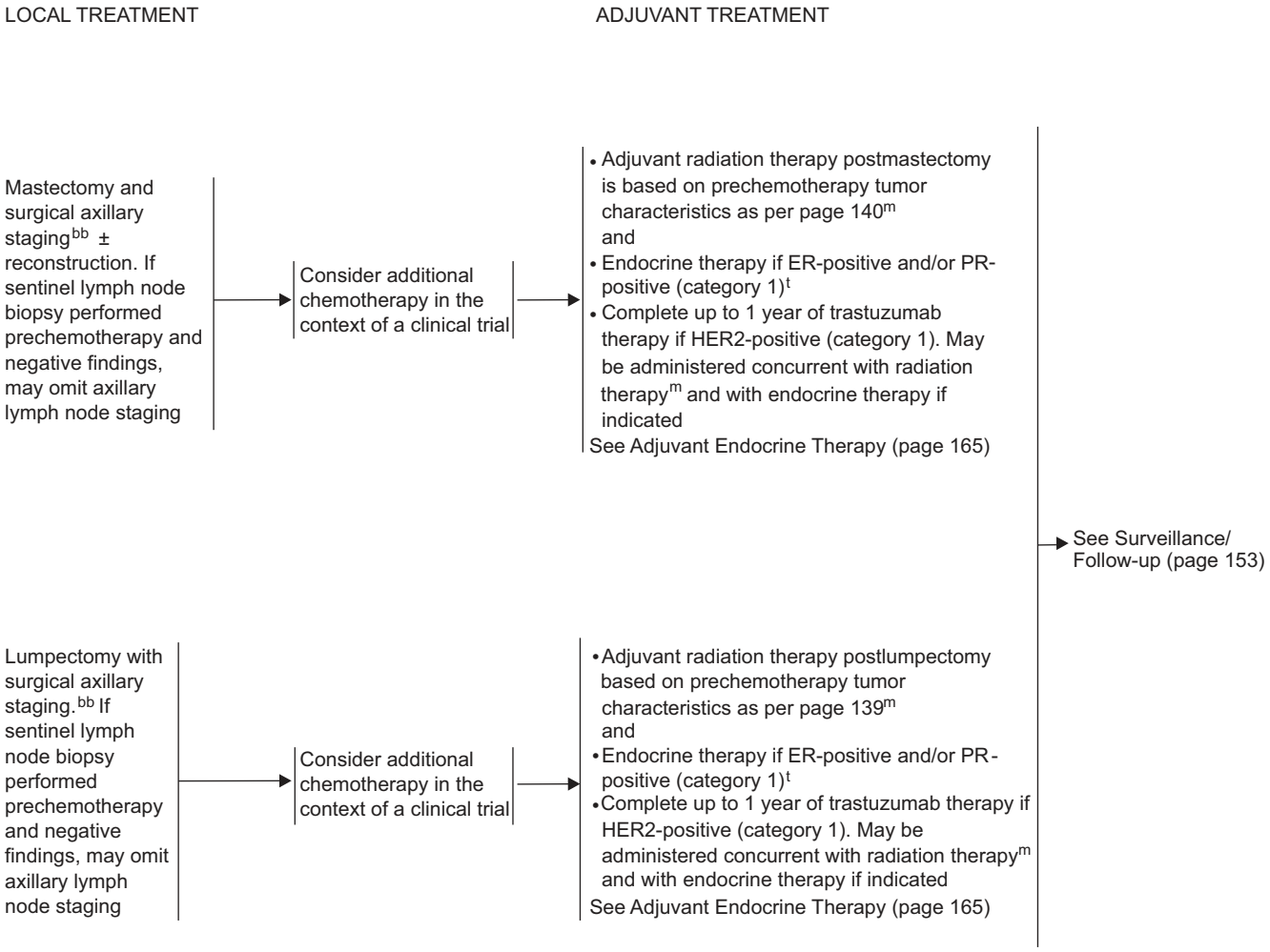
Preoperative Chemotherapy Guideline

PRIMARY TREATMENT



[f] See Surgical Axillary Staging (page 161).
[x] Several combination and single-agent chemotherapy regimens have activity in the preoperative setting. In general, the chemotherapy regimens recommended in the adjuvant setting (see pages 166-170) may be considered in the preoperative setting. If treated with endocrine therapy, an aromatase inhibitor is preferred for postmenopausal women.
[y] Patients with HER2-positive tumors should be treated with preoperative chemotherapy incorporating trastuzumab for at least 9 weeks of preoperative therapy (see pages 166-170).
[z] Administration of all chemotherapy before surgery is preferred.
[aa] Definition of Menopause (see page 171).

Preoperative Chemotherapy Guideline



[m] See Principles of Radiation Therapy (page 164).
[t] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy after chemotherapy. The benefits of chemotherapy and endocrine therapy are additive. However, the absolute benefit from chemotherapy may be small. The decision to add chemotherapy to endocrine therapy should be individualized, especially in those with a favorable prognosis in whom the incremental benefit of chemotherapy may be smaller. Available data suggest sequential or concurrent endocrine therapy with radiation therapy is acceptable.
[bb] Axillary staging may include sentinel node biopsy (category 3) or level I/II dissection.

LOCALLY ADVANCED INVASIVE BREAST CANCER (NONINFLAMMATORY)

CLINICAL STAGE

WORKUP

Stage IIIA
T0,N2,M0
T1,N2,M0
T2,N2,M0
T3,N2,M0

(Stage IIIA with T3,N1,M0 disease, see page 138)

Stage IIIB
T4,N0,M0
T4,N1,M0
T4,N2,M0

Stage IIIC
Any T,N3,M0

Stage IV
Any T,any N,M1 → See Initial Workup for Stage IV Disease (page 153)

General workup, including:
- History and physical
- CBC, platelets
- Liver function tests and alkaline phosphatase
- Diagnostic bilateral mammogram, ultrasound as necessary
- Pathology review[a]
- Determination of tumor ER/PR status and HER2 status[b]
- Genetic counseling if patient is high risk for hereditary breast cancer[c]

Optional additional studies for breast imaging:
- Breast MRI

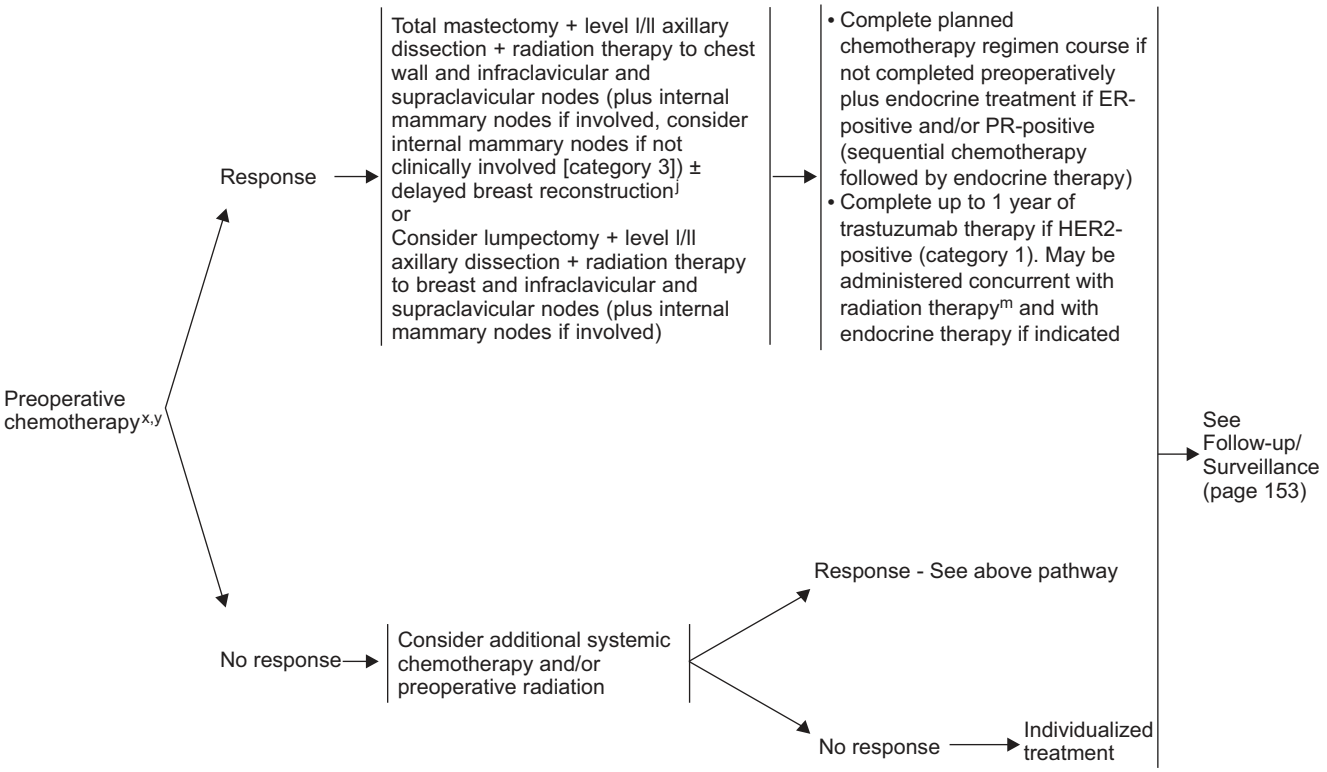
If clinical stage IIIA (T3,N1,M0) consider:
- Bone scan (category 2B)
- Abdominal ± pelvis CT or US or MRI
- Chest imaging

Optional studies as directed by signs and symptoms:
- Bone scan indicated if localized bone pain or elevated alkaline phosphatase
- Abdominal ± pelvis CT or US or MRI if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, abnormal physical examination of the abdomen or pelvis
- Chest imaging (if pulmonary symptoms are present)
- FDG PET/CT scan (category 2B)[e]
- Consider fertility counseling if indicated[f]

→ See Preoperative Chemotherapy and Locoregional Treatment (page 152)

[a] The panel endorses the College of American Pathology Protocol for pathology reporting for all invasive and non-invasive carcinomas of the breast. Available at http://www.cap.org.
[b] See Principles of HER2 Testing (page 159).
[c] See 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.
[d] See Principles of Dedicated Breast MRI Testing (page 160)
[e] The use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease. FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.
[f] See Fertility and Birth Control After Adjuvant Breast Cancer Treatment (page 160).

PREOPERATIVE CHEMOTHERAPY FOR LOCALLY ADVANCED INVASIVE BREAST CANCER (NONINFLAMMATORY)



m See Principles of Radiation Therapy (page 164).
j See Principles of Breast Reconstruction Following Surgery (page 163).
x Several combination and single-agent chemotherapy regimens have activity in the preoperative setting. The chemotherapy regimens recommended in the adjuvant setting (see pages 166-170) may be considered in the preoperative setting. If treated with endocrine therapy, an aromatase inhibitor is preferred for postmenopausal women.
y Patients with HER2-positive tumors should be treated with preoperative chemotherapy incorporating trastuzumab for at least 9 weeks of preoperative therapy (see pages 166-170).

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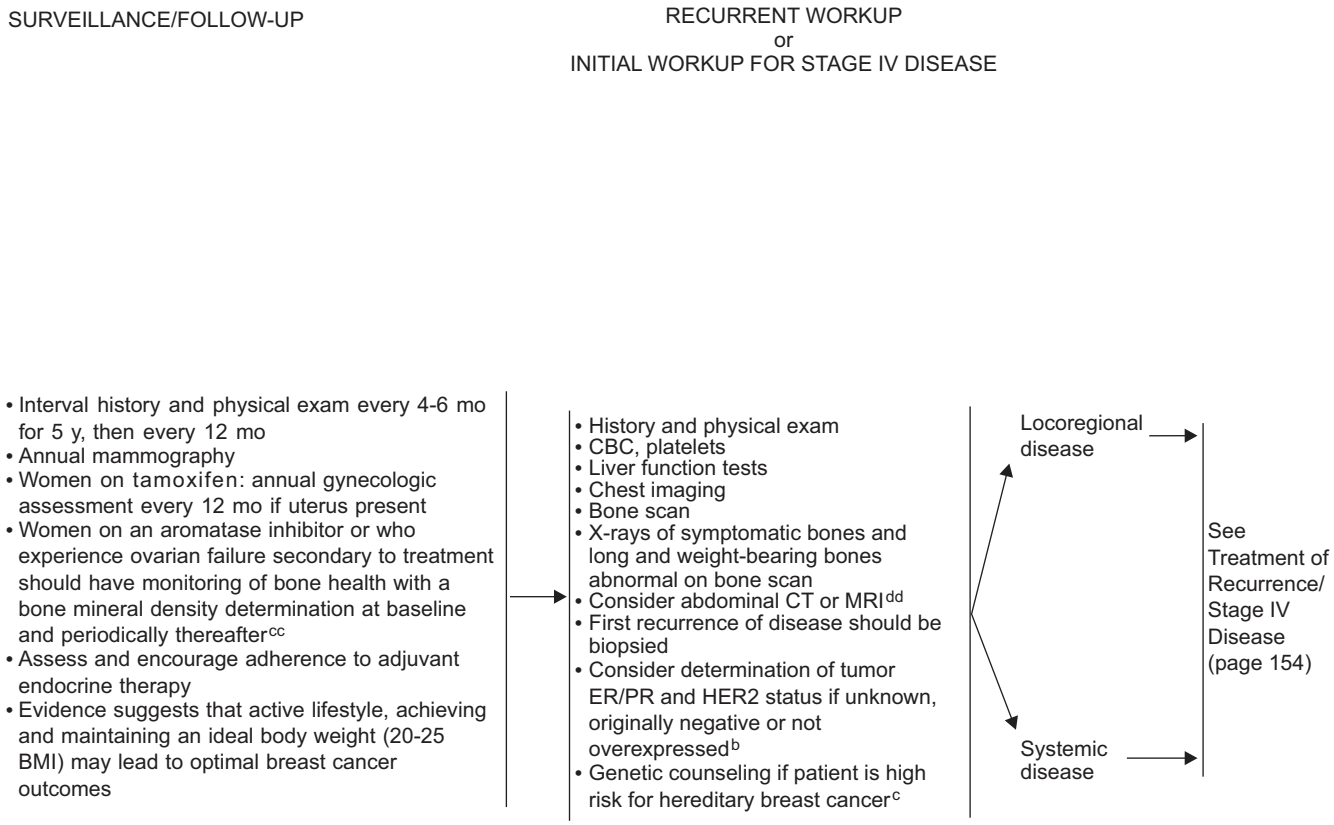


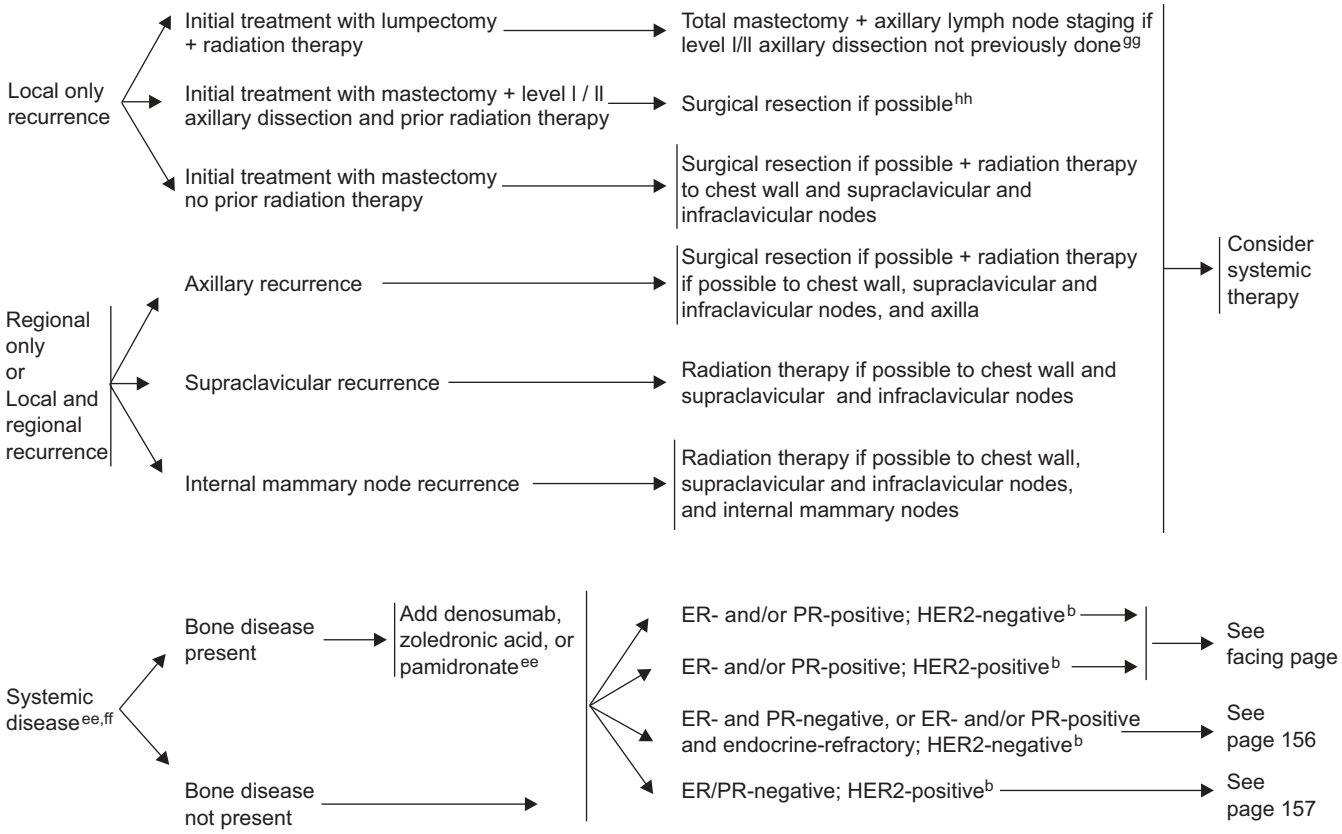
[b] See Principles of HER2 Testing (page 159).

[c] See 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.

[cc] The use of estrogen, progesterone, or selective estrogen receptor modulators to treat osteoporosis or osteopenia in women with breast cancer is discouraged. The use of a bisphosphonate is generally the preferred intervention to improve bone mineral density. Optimal duration of bisphosphonate therapy has not been established. Factors to consider for duration of antiosteoporosis therapy include bone mineral density, response to therapy, and risk factors for continued bone loss or fracture. Women treated with a bisphosphonate should undergo a dental examination with preventive dentistry before the initiation of therapy, and should take supplemental calcium and vitamin D.

[dd] The use of PET or PET/CT scanning should generally be discouraged for the evaluation of metastatic disease except in those clinical situations where other staging studies are equivocal or suspicious. Even in these situations, biopsy of equivocal or suspicious sites is more likely to provide useful information.

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE



Surgery, radiation, or regional chemotherapy (e.g., intrathecal methotrexate) indicated for localized clinical scenarios:

1. Brain metastases
2. Leptomeningeal disease
3. Choroid metastases
4. Pleural effusion
5. Pericardial effusion
6. Biliary obstruction
7. Ureteral obstruction
8. Impending pathologic fracture
9. Pathologic fracture
10. Cord compression
11. Localized painful bone or soft-tissue disease
12. Chest wall disease ± hyperthermia (category 3) if radiation therapy used

[b] See Principles of HER2 Testing (page 159).

[ee] Denosumab, zolendronic acid, or pamidronate (all with calcium and vitamin D supplementation) should be given (category 1) in addition to chemotherapy or endocrine therapy if bone metastasis is present, expected survival is ≥ 3 mo, and renal function is adequate. Patients should undergo a dental examination with preventive dentistry before initiation of this therapy. The optimal schedule and duration of denosumab, zoledronic acid, or pamidronate are unknown.

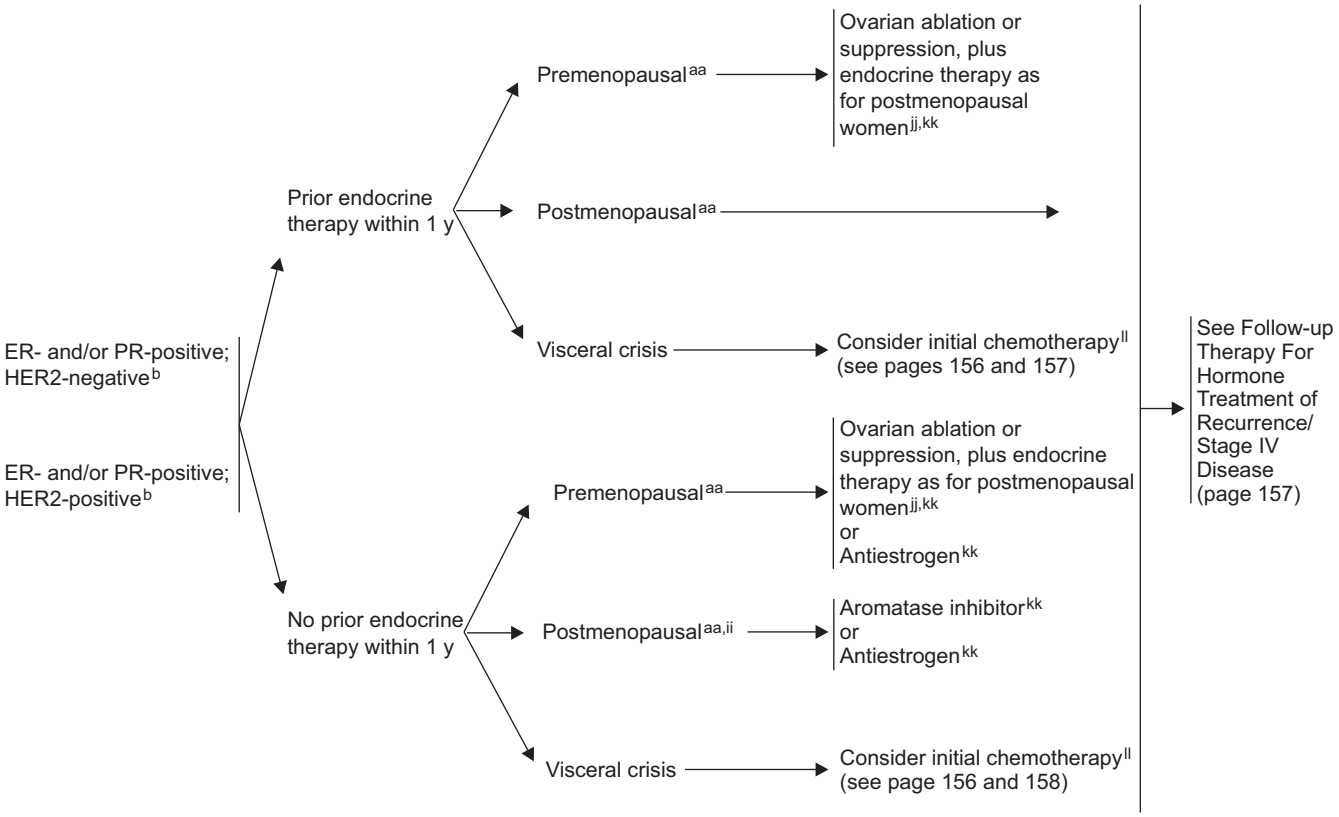
[ff] See NCCN Guidelines for Palliative Care; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

[gg] In women with a local breast recurrence after breast-conserving surgery who had a prior sentinel lymph node biopsy (SLNB), a repeat SLNB may be technically possible. The accuracy of repeat SLNB is unproven, and the prognostic significance of repeat SLNB after mastectomy is unknown and its use discouraged.

[hh] If not technically resectable, consider systemic therapy to best response, then resect if possible.

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE

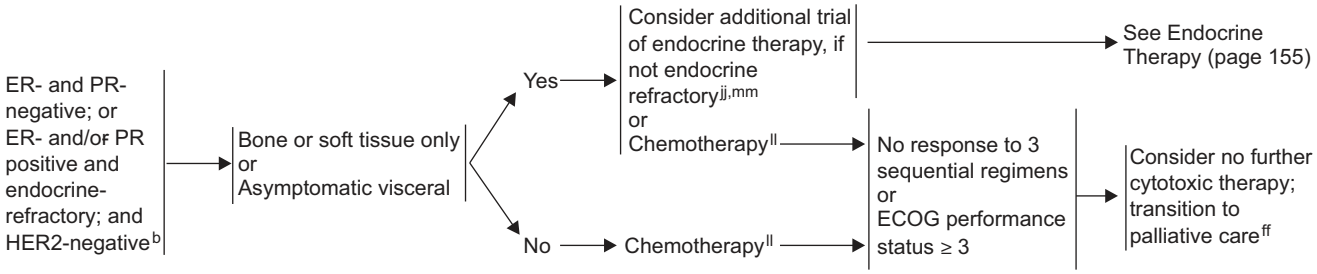
ER- and/or PR-POSITIVE; HER2-NEGATIVE OR -POSITIVE



[b] See Principles of HER2 Testing (page 159).
[aa] Definition of Menopause (page 171).
[ii] Limited studies document a progression-free survival advantage with adding trastuzumab or lapatinib to aromatase inhibition in postmenopausal patients with ER-positive, HER2-positive disease. However, no overall survival advantage has been shown.
[jj] See Subsequent Endocrine Therapy (page 171).
[kk] Women presenting at initial diagnosis with metastatic disease may benefit from the performance of local breast surgery and/or radiation therapy. Generally this palliative local therapy should be considered only after response to initial systemic therapy.
[ll] See Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (pages 172-177).

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE

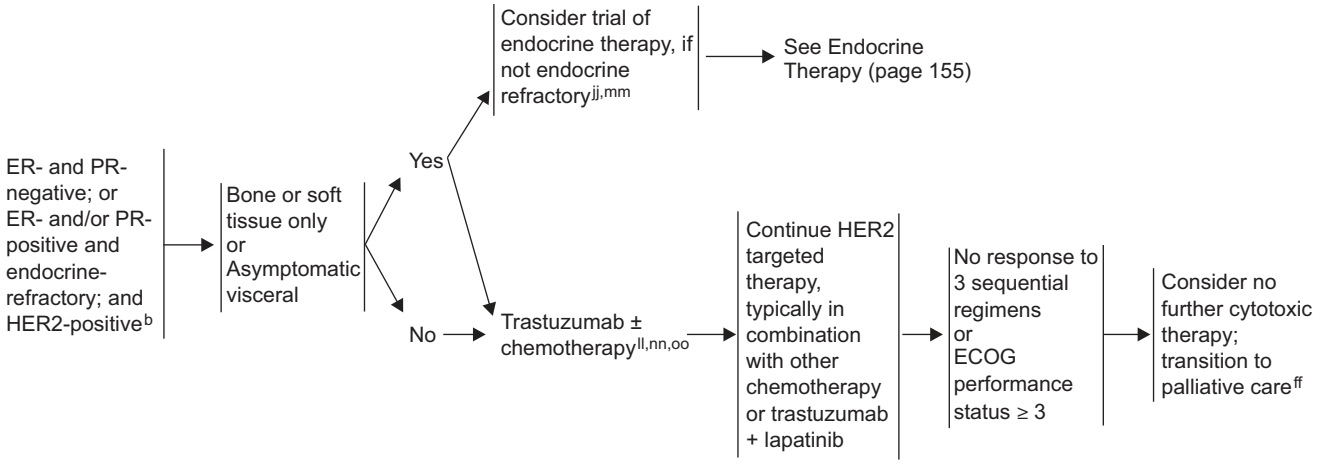
ER- and PR-NEGATIVE; or ER- and/or PR-POSITIVE and ENDOCRINE-REFRACTORY; HER2-NEGATIVE



[b] See Principles of HER2 Testing (page 159).
[ff] See NCCN Guidelines for Palliative Care; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.
[jj] See Subsequent Endocrine Therapy (page 171).
[ll] See Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (pages 172-177).
[mm] False-negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy with its low attendant toxicity may be considered in patients with nonvisceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a hormone receptor–positive tumor (e.g., long disease-free interval, limited sites of recurrence, indolent disease, older age).

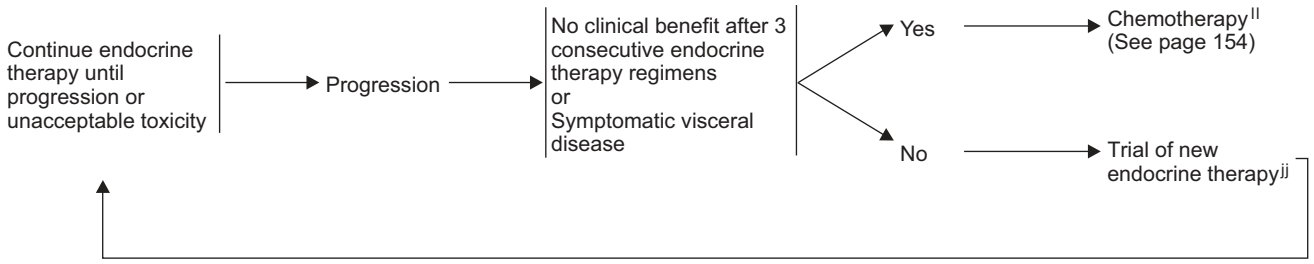
SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE

ER- and PR-NEGATIVE; or ER- and/or PR-POSITIVE and ENDOCRINE-REFRACTORY; and HER2-POSITIVE



[b] See Principles of HER2 Testing (page 159).
[ff] See NCCN Guidelines for Palliative Care; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.
[jj] See Subsequent Endocrine Therapy (page 171).
[ll] See Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (pages 172-177).
[mm] False-negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy with its low attendant toxicity may be considered in patients with nonvisceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a hormone receptor–positive tumor (e.g., long disease-free interval, limited sites of recurrence, indolent disease, older age).
[nn] Continued trastuzumab after progression on first-line trastuzumab containing chemotherapy for metastatic breast cancer. The optimal duration of trastuzumab in patients with long-term control of disease is unknown.
[oo] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity.

FOLLOW-UP THERAPY FOR ENDOCRINE TREATMENT OF RECURRENT OR STAGE IV DISEASE



[jj] See Subsequent Endocrine Therapy (page 171).
[ll] See Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (pages 172-177).

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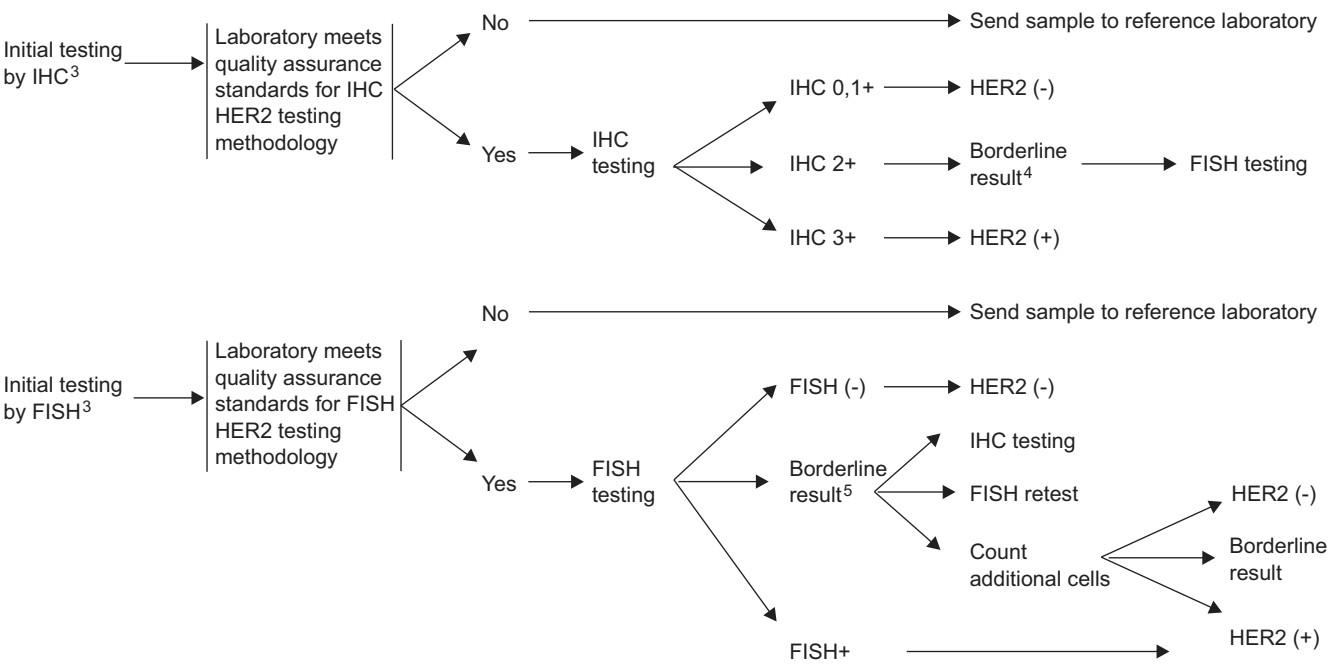
PRINCIPLES OF HER2 TESTING[1,2]



[1] See also, Carlson RW, Moench SJ, Hammond MEH, et al. HER2 testing in breast cancer: NCCN task force report and recommendations . J Natl Compr Canc Netw 2006;4(Suppl 3):S1-S24.

[2] HER2 testing should be performed only in laboratories accredited to perform this testing. Ongoing proficiency testing and full reporting of HER2 assay methods and results are required. A laboratory may perform only the tests that have been shown to conform to these quality assurance standards. All other HER2 testing should be sent to a qualified reference laboratory.

[3] Either an immunohistochemistry (IHC) assay or a fluorescence in situ hybridization (FISH) assay can be used to make an initial assessment of HER2 tumor status. All HER2 assays, whether FDA-approved or not, must be validated. Validation of a HER2 test is defined as at least 95% concordance when the testing method performed in a laboratory is compared with one of the following: a validated HER2 testing method performed in the same laboratory; a validated HER2 testing method performed in another laboratory; or validated reference laboratory results. Borderline samples should not be included in the validation study. These algorithms are based on the assumption that all validated HER2 tests have been shown to be at least 95% concordant with the complementary form of the HER2 test, either by direct testing or association with the levels of concordance between complementary testing achieved by the validating laboratory.

[4] Borderline IHC samples (e.g., IHC 2+) are subjected to reflex testing by a validated complementary (e.g., FISH) method that has shown at least 95% concordance between IHC 0, 1+ results and FISH non-amplified results, and IHC 3+ results and FISH amplified results.

[5] Borderline FISH samples (e.g., an average HER2 gene/chromosome 17 ratio of 1.8-2.2 or an average HER2 gene copy number of > 4 to < 6) should undergo: counting of additional cells, retesting by FISH, or reflex testing by a validated IHC method that is at least 95% concordant with FISH as described above.

PRINCIPLES OF DEDICATED BREAST MRI TESTING

See NCCN Guidelines for Breast Screening and Diagnosis for indications for screening MRI in women at increased breast cancer risk (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Personnel, Facility, and Equipment

- Breast MRI examinations should be performed and interpreted by an expert breast imaging team working in concert with the multidisciplinary treatment team.
- Breast MRI examinations require a dedicated breast coil and breast imaging radiologists familiar with the optimal timing sequences and other technical details for image interpretation. The imaging center should have the ability to perform MRI-guided needle sampling and/or wire localization of MRI detected findings.

Clinical Indications and Applications

- May be used for staging evaluation to define extent of cancer or presence of multifocal or multicentric cancer in the ipsilateral breast, or as screening of the contralateral breast cancer at initial diagnosis (category 2B). No data show that using MRI in choosing local therapy improves outcome (local recurrence or survival).
- May be helpful for breast cancer evaluation before and after neoadjuvant therapy to define extent of disease, response to treatment, and potential for breast-conserving therapy.
- May be useful to detect additional disease in women with mammographically dense breast, but available data do not show differential detection rates by any subset by breast pattern (breast density) or disease type (e.g., DCIS, invasive ductal cancer, invasive lobular cancer).
- May be useful to identify primary cancer in women with axillary nodal adenocarcinoma or Paget's disease of the nipple with breast primary not identified on mammography, ultrasound, or physical examination.
- False-positive findings on breast MRI are common. Surgical decisions should not be based solely on the MRI findings. Additional tissue sampling of areas of concern identified by breast MRI is recommended.
- The efficacy of MRI in follow-up screening of women with prior breast cancer is undefined. It should generally be considered only in those whose lifetime risk of a second primary breast cancer is greater than 20% based on models largely dependent on family history, such as in those with the risk associated with inherited susceptibility to breast cancer.

Houssami N, Ciatto S, Macaskill P, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol 2008;26:3248-3258.

FERTILITY AND BIRTH CONTROL AFTER ADJUVANT BREAST CANCER TREATMENT

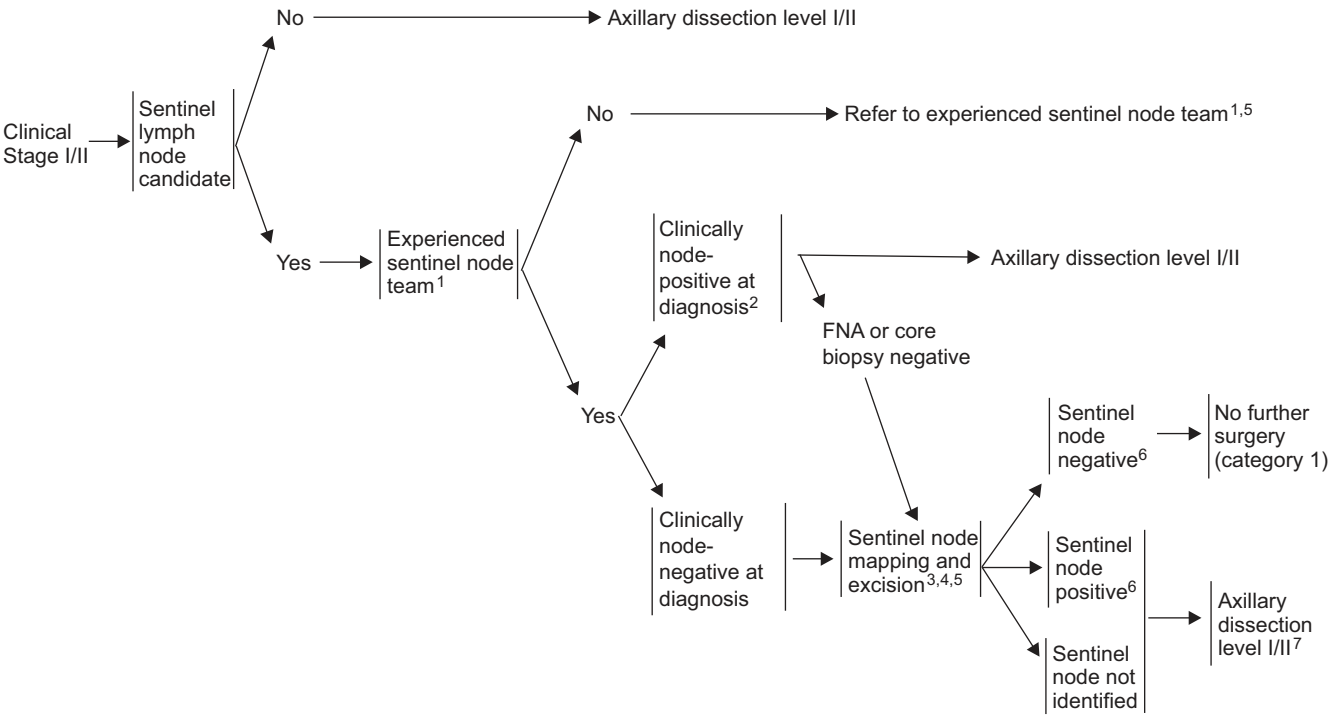
- Although amenorrhea frequently occurs during or after chemotherapy, most women younger than 35 y seem to resume menses within 2 y of finishing adjuvant chemotherapy.
- Menses and fertility are not necessarily linked. Absence of regular menses, particularly if the patient is taking tamoxifen, does not necessarily imply lack of fertility. Conversely, the presence of menses does not guarantee fertility. Limited data are available on continued fertility after chemotherapy.
- Patients should not become pregnant during treatment with radiation therapy, chemotherapy, or endocrine therapy.
- Although data are limited, hormone-based birth control is discouraged regardless of the hormone receptor status of the patient's cancer.
- Alternative methods of birth control include intrauterine devices (IUD), and barrier methods, or for patients with no intent for future pregnancies, tubal ligation, or vasectomy for the partner.
- No therapy has been shown to preserve fertility in patients undergoing chemotherapy.
- Patients who may desire future pregnancies should be referred to fertility specialists before chemotherapy.
- Breast feeding after breast-conserving cancer treatment is not contraindicated. However, the quantity and quality of breast milk produced by the conserved breast may not be sufficient or may be lacking some of the nutrients needed. Breast feeding during active treatment with chemotherapy and endocrine therapy is not recommended.

AXILLARY LYMPH NODE STAGING

In the absence of definitive data showing superior survival from the performance of axillary lymph node dissection, axillary lymph node dissection may be considered optional in patients who have particularly favorable tumors, those for whom the selection of adjuvant systemic therapy is unlikely to be affected, those who are elderly, or those with serious comorbid conditions. The axillary dissection should be extended to include level III nodes only if gross disease is apparent in the level II nodes.

Sentinel lymph node biopsy is the preferred method of axillary lymph node staging if there is an experienced sentinel node team and the patient is an appropriate sentinel lymph node biopsy candidate (see facing page).

SURGICAL AXILLARY STAGING - STAGE I, IIA, AND IIB



[1] Sentinel node team must have documented experience with sentinel node biopsy in breast cancer. Team includes surgeon, radiologists, nuclear medicine physician, and pathologist, and prior discussion with medical and radiation oncologists on use of sentinel node for treatment decisions.
[2] Consider pathologic confirmation of malignancy in clinically positive nodes using ultrasound-guided FNA or core biopsy in determining if patient needs axillary lymph node dissection.
[3] Axillary sentinel node biopsy in all cases; internal mammary sentinel node biopsy optional if drainage maps to internal mammary nodes (category 3).
[4] Sentinel lymph node mapping injections may be peritumoral, subareolar, or subdermal. However, only peritumoral injections map to the internal mammary lymph node(s).
[5] Results of randomized clinical trials indicate that there is a lower risk of mobidity associated with sentinel node mapping and excision than with level I/II axillary dissection.
[6] Sentinel node involvement is defined by multilevel node sectioning with hematoxylin and eosin (H&E) staining. Cytokeratin IHC may be used for equivocal cases on H&E. Routine cytokeratin IHC to define node involvement is not recommended in clinical decision-making.
[7] Data from a single, randomized trial suggest that complete axillary lymph node dissection in women with clinically node negative T1-T2 tumors, with fewer than 3 involved sentinel lymph nodes, and who are undergoing breast-conserving surgery and whole breast radiation results in more morbidity, no improvement in locoregional recurrence rates, and no difference in overall survival compared with sentinel lymph node procedure alone.

MARGIN STATUS IN INFILTRATING CARCINOMA

The use of breast-conserving therapy is predicated on achieving a pathologically negative margin of resection. When a positive margin should generally undergo further surgery—either a reexcision to achieve a negative margin or a mastectomy. If reexcision is technically feasible to allow for breast-conserving therapy, this can be performed through resection of the involved margin guided by the orientation of the initial resection specimen, or reexcision of the entire original excision cavity. If multiple margins remain positive, mastectomy may be required for optimal local control.

It may be reasonable to treat selected cases with breast-conserving therapy with a microscopically focally positive margin in the absence of an extensive intraductal component.[1] For these patients, the use of a higher radiation boost dose to the tumor bed should be considered.

Margins should be evaluated on all surgical specimens from breast conserving surgery. Requirements for optimal margin evaluation include:

- Orientation of the surgical specimens
- Description of the gross and microscopic margin status
- Reporting of the distance, orientation, and type of tumor (invasive or DCIS) in relation to the closest margin

SPECIAL CONSIDERATIONS TO BREAST-CONSERVING THERAPY REQUIRING RADIATION THERAPY

Contraindications for breast-conserving therapy requiring radiation therapy include:

Absolute:

- Prior radiation therapy to the breast or chest wall
- Radiation therapy during pregnancy
- Diffuse suspicious or malignant appearing microcalcifications
- Widespread disease that cannot be incorporated by local excision through a single incision that achieves negative margins with a satisfactory cosmetic result
- Positive pathologic margin[2]

Relative:

- Active connective tissue disease involving the skin (especially scleroderma and lupus)
- Tumors > 5 cm (category 2B)
- Focally positive margin[2]
- Women aged ≤ 35 y or premenopausal women with a known BRCA1/2 mutation:
  - ➤ May have an increased risk of ipsilateral breast recurrence or contralateral breast cancer with breast-conserving therapy
  - ➤ Prophylactic bilateral mastectomy for risk reduction may be considered (See NCCN Guidelines for Breast Cancer Risk Reduction; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org)

[1] An extensive intraductal component is defined as an infiltrating ductal cancer in which > 25% of the tumor volume is DCIS and DCIS extends beyond the invasive cancer into surrounding normal breast parenchyma.
[2] See Margin Status in Infiltrating Carcinoma (see above section).

PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

- The breast can be reconstructed in conjunction with mastectomy using breast implants or autologous tissue ("flaps"), or a combination of these (e.g., latissimus/implant composite reconstructions).
- Breast reconstruction for mastectomy can be performed at the same time as mastectomy ("immediate") or at some time after the completion of cancer treatment ("delayed").
- As with any mastectomy, there is a risk of local and regional cancer recurrence, and evidence suggests skin-sparing mastectomy is probably equivalent to standard mastectomy in this regard. Skin-sparing mastectomy should be performed by an experienced breast surgery team that works in a coordinated, multidisciplinary fashion to guide proper patient selection for skin-sparing mastectomy, determine optimal sequencing of the reconstructive procedure(s) in relation to adjuvant therapies, and perform a resection that achieves appropriate surgical margins. Postmastectomy radiation as outlined in these guidelines should be applied in cases treated with skin-sparing mastectomy. The nipple-areolar complex is sacrificed with skin-sparing mastectomy for cancer therapy. Current data are inadequate to support the use of nipple-areolar complex sparing procedures for breast cancer therapy outside the confines of a prospective clinical trial.
- When postmastectomy radiation is required, delayed reconstruction is generally preferred after completion of radiation therapy in autologous tissue reconstruction because of reported loss in reconstruction cosmesis (category 2B). When implant reconstruction is used, immediate rather than delayed reconstruction is preferred to avoid tissue expansion of radiated skin flaps. Immediate implant reconstruction in patients requiring postoperative radiation has an increased rate of capsular contracture. Surgery to exchange the tissue expanders with permanent implants can be performed before radiation or after completion of radiation therapy. Some experienced breast cancer teams have used protocols in which immediate reconstructions are followed by radiation therapy (category 2B). Tissue expansion of irradiated skin can result in a significantly increased risk of capsular contracture, malposition, poor cosmesis, and implant exposure. In the previously radiated patient, the use of tissue expanders/implants is relatively contraindicated.
- Reconstruction selection is based on an assessment of cancer treatment, patient body habitus, smoking history, comorbidities, and patient concerns. Smoking increases the risk of complications for all types of breast reconstruction, whether with implant or flap. Smoking is therefore considered a relative contraindication to breast reconstruction, and patients should be made aware of increased rates of wound healing complications and partial or complete flap failure among smokers.
- An evaluation of the likely cosmetic outcome of lumpectomy should be performed before surgery.
- Women who are not satisfied with the cosmetic outcome after completion of breast cancer treatment should be offered a plastic surgery consultation.

PRINCIPLES OF RADIATION THERAPY

Whole Breast Radiation:
Target definition includes most of the breast tissue, and is best performed through both clinical assessment and CT-based treatment planning. A uniform dose distribution and minimal normal tissue toxicity are the goals and can be accomplished using compensators such as wedges; forward planning using segments; intensity-modulated radiation therapy (IMRT); respiratory gating; and prone positioning. The breast should receive a dose of 45 to 50 Gy given in 1.8 to 2 Gy per fraction, or 42.5 Gy at 2.66 Gy per fraction. A boost to the tumor bed is recommended in patients at higher risk for local failure, (age < 50 y, positive axillary nodes, lymphovascular invasion, or close margins). This can be achieved with brachytherapy or electron beam or photon fields. Typical doses are 10 to 16 Gy at 2 Gy per fraction. All dose schedules are given 5 days per week.

Chest Wall Radiation (including breast reconstruction):
The target includes the ipsilateral chest wall, mastectomy scar, and drain sites where possible. Depending on whether the patient has undergone reconstruction, several techniques using photons and/or electrons are appropriate. CT-based treatment planning is encouraged to identify lung and heart volumes and minimize exposure of these organs. Special consideration should be given to the use of bolus material when photon fields are used to ensure the skin dose is adequate.

Regional Nodal Radiation:
Target delineation is best achieved through CT-based treatment planning. For the paraclavicular and axillary nodes, prescription depth varies based on the size of the patient. For internal mammary node identification, the internal mammary artery and vein location can be used as a surrogate for the nodal locations, which usually are not visible on imaging.

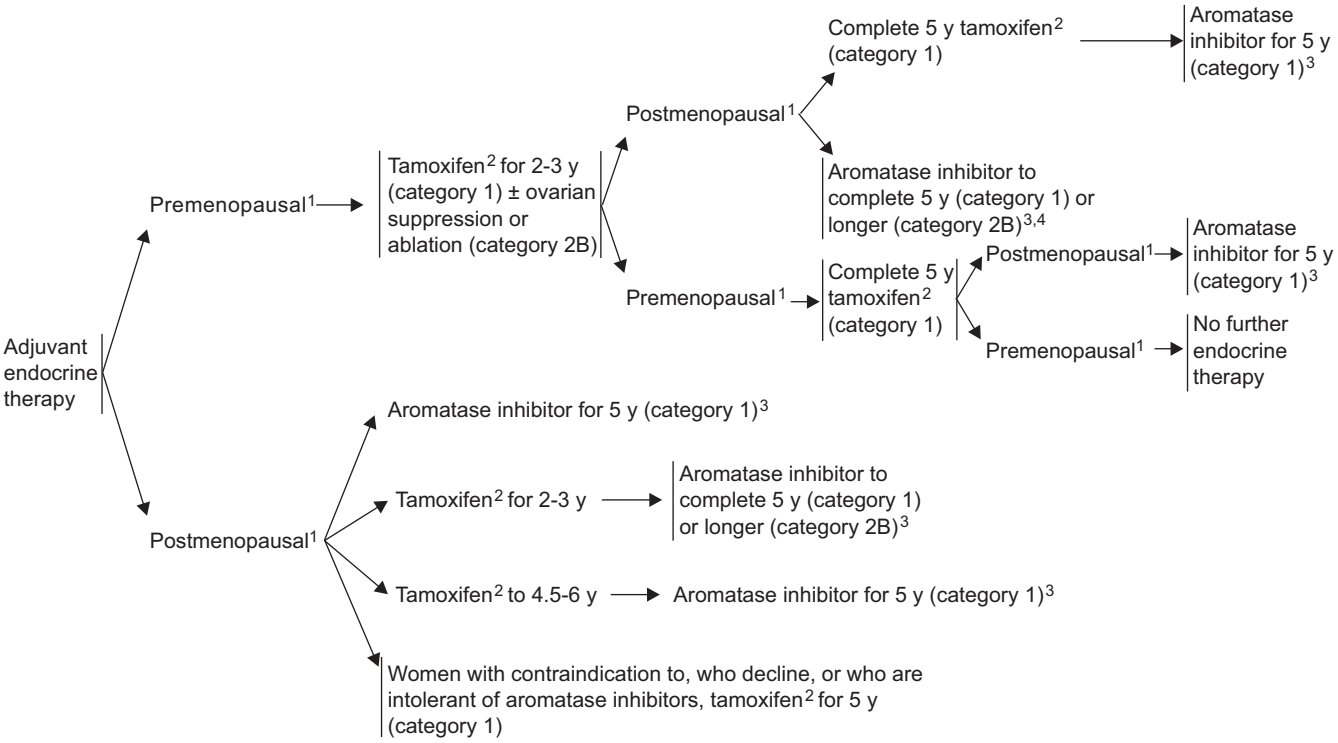
Dose is 50 to 50.4 Gy, given in 1.8 to 2.0 Gy per fraction size (± scar boost at 2 Gy per fraction to a total dose of approximately 60 Gy); all dose schedules given 5 days per week. If internal mammary lymph nodes are clinically or pathologically positive, radiation therapy should be given to the internal mammary nodes, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT-based treatment planning should occur whenever radiation therapy is delivered to the internal mammary lymph node field.

Accelerated Partial Breast Irradiation:
Preliminary studies of accelerated partial breast irradiation (APBI) suggest that selected patients with early-stage breast cancer may have comparable rates of control to those treated with standard whole breast radiation therapy. Follow-up, however, is limited and studies are ongoing. Patients are encouraged to participate in clinical trials. If not trial-eligible, per the consensus statement from the American Society for Radiation Oncology (ASTRO), patients who may be suitable for APBI are women 60 y and older who are not carriers of BRCA1/2 mutation treated with primary surgery for a unifocal T1,N0 ER-positive cancer Histology should be infiltrating ductal or a favorable ductal subtype and should not be associated with EIC or LCIS, and margins should be negative. 34 Gy in 10 fractions delivered twice per day with brachytherapy or 38.5 Gy in 10 fractions delivered twice per day with external-beam photon therapy is prescribed to the tumor bed. Other fractionation schemes are currently under investigation.

Optimizing Delivery of Individual Therapy:
It is important to individualize delivery of radiation therapy and considerations such as patient positioning (i.e., prone vs. supine) during administration of radiation therapy.

Neoadjuvant Chemotherapy:
Indications for radiation therapy and fields of treatment should be based on the pretreatment tumor characteristics in patients treated with neoadjuvant chemotherapy.

ADJUVANT ENDOCRINE THERAPY



[1] See Definition of Menopause (page 171).
[2] Some selective serotonin reuptake inhibitors, such as fluoxetine and paroxetine, decrease the formation of endoxifen, an active metabolite of tamoxifen, and may impact its efficacy. Caution is advised about coadministration of these drugs with tamoxifen. However, citalopram and venlafaxine seem to have minimal impact on tamoxifen metabolism. Based on current data, the panel currently does not endorse routine CYP2D6 testing for women being considered for tamoxifen therapy.
[3] The panel believes the 3 selective aromatase inhibitors (anastrozole, letrozole, exemestane) have similar antitumor efficacy and similar toxicity profiles. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.
[4] This specific patient subset was not included in the trials of aromatase inhibitors given sequentially with adjuvant tamoxifen. Some women who seem to become postmenopausal on tamoxifen therapy experience resumption of ovarian function after discontinuation of tamoxifen and initiation of an aromatase inhibitor. Therefore, serial monitoring of plasma estradiol and follicular-stimulating hormone levels is encouraged in this clinical setting. Should ovarian function resume, the aromatase inhibitor should be discontinued and tamoxifen resumed. See Definition of Menopause (page 171).

NEOADJUVANT/ADJUVANT CHEMOTHERAPY[1–5]

NON–TRASTUZUMAB-CONTAINING REGIMENS (all category 1)

Preferred Adjuvant Regimens

- TAC (docetaxel/doxorubicin/cyclophosphamide)
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 wk
- AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel
- TC (docetaxel/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)

Other Adjuvant Regimens

- FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide)
- FEC/CEF (cyclophosphamide/epirubicin/fluorouracil)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC followed by docetaxel every 3 wk
- EC (epirubicin/cyclophosphamide)
- A followed by T followed by C (doxorubicin followed by paclitaxel followed by cyclophosphamide) every 2 wk with filgrastim support
- FEC followed by T (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel
- FEC (fluorouracil/epirubicin/cyclophosphamide) followed by weekly paclitaxel

TRASTUZUMAB-CONTAINING REGIMENS (all category 1)

Preferred Adjuvant Regimens

- AC followed by T + concurrent trastuzumab (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules)
- TCH (docetaxel, carboplatin, trastuzumab)

Other Adjuvant Regimens

- Docetaxel + trastuzumab followed by FEC (fluorouracil/epirubicin/cyclophosphamide) Chemotherapy followed by trastuzumab sequentially
- AC followed by docetaxel + trastuzumab

Neoadjuvant Regimens

- T + trastuzumab followed by CEF + trastuzumab (paclitaxel plus trastuzumab followed by cyclophosphamide/epirubicin/fluorouracil plus trastuzumab)

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities, individual patient variability, prior treatment, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

[1]Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to non–anthracycline-based regimens in patients with HER2-positive tumors.

[2]In patients with HER2-positive and axillary lymph node–positive breast cancer, trastuzumab should be incorporated into the adjuvant therapy (category 1). Trastuzumab should also be considered for patients with HER2-positive, lymph node–negative tumors 1 cm or larger (category 1). Trastuzumab may be given beginning either concurrent with paclitaxel as part of the AC followed by paclitaxel regimen, or alternatively after the completion of chemotherapy. Trastuzumab should not be given concurrent with an anthracycline because of cardiac toxicity, except as part of the neoadjuvant trastuzumab with paclitaxel followed by CEF regimen. Trastuzumab should be given for 1 y (except with the docetaxel + trastuzumab followed by FEC regimen, in which trastuzumab is given for 9 wk), with cardiac monitoring, and using either the weekly or the every-3-weekly schedule.

[3]CMF and radiation therapy may be given concurrently, or the CMF may be given first. All other chemotherapy regimens should be given before radiotherapy.

[4]Chemotherapy and tamoxifen used as adjuvant therapy should be given sequentially with tamoxifen after chemotherapy.

[5]Randomized clinical trials show that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.

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.

NON–TRASTUZUMAB-CONTAINING COMBINATIONS

Preferred Adjuvant Regimens

TAC chemotherapy[1]
- Docetaxel, 75 mg/m^2 IV, day 1
- Doxorubicin, 50 mg/m^2 IV, day 1
- Cyclophosphamide, 500 mg/m^2 IV, day 1

Cycled every 21 days for 6 cycles
(All cycles are with filgrastim support)

Dose-dense AC followed by paclitaxel chemotherapy[15]
- Doxorubicin, 60 mg/m^2 IV, day 1
- Cyclophosphamide, 600 mg/m^2 IV, day 1

Cycled every 14 days for 4 cycles
Followed by
- Paclitaxel, 175 mg/m^2 by 3-h IV infusion, day 1

Cycled every 14 days for 4 cycles
(All cycles are with filgrastim support)

AC followed by paclitaxel chemotherapy[3–5]
- Doxorubicin, 60 mg/m^2 IV, day 1
- Cyclophosphamide, 600 mg/m^2 IV, day 1
- Cycled every 21 days for 4 cycles

Followed by
- Paclitaxel, 80 mg/m^2 by 1-h IV infusion weekly, for 12 wk

TC chemotherapy[6]
- Docetaxel, 75 mg/m^2 IV, day 1
- Cyclophosphamide, 600 mg/m^2 IV, day 1

Cycled every 21 days for 4 cycles

AC chemotherapy[7]
- Doxorubicin, 60 mg/m^2 IV, day 1
- Cyclophosphamide, 600 mg/m^2 IV, day 1

Cycled every 21 days for 4 cycles

Other Adjuvant Regimens

FAC chemotherapy[8,9]
- 5-Fluorouracil, 500 mg/m^2 IV, days 1 and 8 or days 1 and 4
- Doxorubicin, 50 mg/m^2 IV, day 1 (or by 72-h continuous infusion)
- Cyclophosphamide, 500 mg/m^2 IV, day 1

Cycled every 21 days for 6 cycles

CAF chemotherapy[10]
- Cyclophosphamide, 100 mg/m^2 IV, day 1
- Doxorubicin, 30 mg/m^2 IV, days 1 and 8
- 5-Fluorouracil, 500 mg/m^2 IV, days 1 and 8

Cycled every 28 days for 6 cycles

CEF chemotherapy[11]
- Cyclophosphamide, 75 mg/m^2 PO, days 1-14
- Epirubicin, 60 mg/m^2 IV, days 1 and 8
- 5-Fluorouracil, 500 mg/m^2 IV, days 1 and 8

With cotrimoxazole support
Cycled every 28 days for 6 cycles

CMF chemotherapy[12]
- Cyclophosphamide, 100 mg/m^2 PO, days 1-14
- Methotrexate, 40 mg/m^2 IV, days 1 and 8
- 5-Fluorouracil, 600 mg/m^2 IV, days 1 and 8

Cycled every 28 days for 6 cycles

AC followed by docetaxel chemotherapy[5]
- Doxorubicin, 60 mg/m^2, on day 1
- Cyclophosphamide, 600 mg/m^2 IV, day 1

Cycled every 21 days for 4 cycles
Followed by
- Docetaxel, 100 mg/m^2 IV, on day 1

Cycled every 21 days for 4 cycles

EC chemotherapy[13]
- Epirubicin, 100 mg/m^2 IV, day 1
- Cyclophosphamide, 830 mg/m^2 IV, day 1

Cycled every 21 days for 8 cycles

Dose-dense A-T-C chemotherapy[14]
- Doxorubicin, 60 mg/m^2 IV, day 1

Cycled every 14 days for 4 cycles
Followed by
- Paclitaxel, 175 mg/m^2 by 3-h IV, day 1

Cycled every 14 days for 4 cycles
Followed by
- Cyclophosphamide, 600 mg/m^2 IV, day 1

Cycled every 14 days for 4 cycles
(All cycles are with filgrastim support)

FEC followed by docetaxel chemotherapy[14]
- 5-Fluorouracil, 500 mg/m^2 IV, day 1
- Epirubicin, 100 mg/m^2 IV, day 1
- Cyclophosphamide, 500 mg/m^2, day 1

Cycled every 21 days for 3 cycles
Followed by
- Docetaxel, 100 mg/m^2, day 1

Cycled every 21 days for 3 cycles

FEC followed by weekly paclitaxel[16]
- 5-fluorouracil, 600 mg/m^2 IV, day 1
- Epirubicin, 90 mg/m^2 IV, day 1
- Cyclophosphamide, 600 mg/m^2 IV, day 1

Cycled every 21 days for 4 cycles
Followed by:
- 3 wk of no treatment

Followed by
- Paclitaxel, 100 mg/m^2 IV

Cycled every week for 8 cycles

References available on page 170.

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities, individual patient variability, prior treatment, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

TRASTUZUMAB-CONTAINING COMBINATIONS

Preferred Adjuvant Regimens

AC followed by T chemotherapy with trastuzumab[17]
- Doxorubicin, 60 mg/m^2 IV, day 1
- Cyclophosphamide, 600 mg/m^2 IV, day 1

Cycled every 21 days for 4 cycles
Followed by
Paclitaxel, 80 mg/m^2 by 1-h IV, weekly for 12 wk
With
- Trastuzumab, 4 mg/kg IV, with first dose of paclitaxel

Followed by
- Trastuzumab, 2 mg/kg IV, weekly to complete 1 y of treatment. As an alternative, trastuzumab, 6 mg/kg IV, every 3 wk may be used after completion of paclitaxel, and given to complete 1 y of trastuzumab treatment

Cardiac monitoring at baseline, 3, 6, and 9 mo

Dose-dense AC followed by paclitaxel chemotherapy[2]
- Doxorubicin, 60 mg/m^2 IV, day 1
- Cyclophosphamide, 600 mg/m^2 IV, day 1

Cycled every 14 days for 4 cycles
Followed by
- Paclitaxel, 175 mg/m^2 by 3-h IV infusion, day 1

Cycled every 14 days for 4 cycles
(All cycles are with filgrastim support)
With
- Trastuzumab, 4 mg/kg IV, with first dose of paclitaxel

Followed by
- Trastuzumab, 2 mg/kg IV, weekly to complete 1 y of treatment. As an alternative, trastuzumab, 6 mg/kg IV, every 3 wk may be used after completion of paclitaxel, and given to complete 1 y of trastuzumab treatment

Cardiac monitoring at baseline, 3, 6, and 9 mo

AC followed by T chemotherapy with trastuzumab[17]
- Doxorubicin, 60 mg/m^2 IV, day 1
- Cyclophosphamide, 600 mg/m^2 IV, day 1

Cycled every 21 days for 4 cycles
Followed by
- Paclitaxel, 175 mg/m^2 by 3-h IV, day 1

Cycled every 21 days for 4 cycles
With
- Trastuzumab, 4 mg/kg IV, with first dose of paclitaxel

Followed by
- Trastuzumab, 2 mg/kg IV, weekly to complete 1 y of treatment. As an alternative, trastuzumab, 6 mg/kg IV, every 3 wk may be used following the completion of paclitaxel, and given to complete 1 y of trastuzumab treatment

Cardiac monitoring at baseline, 3, 6, and 9 mo

TCH chemotherapy[18]
- Docetaxel, 75 mg/m^2 IV, day 1

Followed by
- Carboplatin, AUC 6 IV, day 1

Cycled every 21 days for 6 cycles
With
- Trastuzumab, 4 mg/kg, wk 1

Followed by
- Trastuzumab, 2 mg/kg, for 17 wk

Followed by
- Trastuzumab, 6 mg/kg IV, every 3 wk to complete 1 y of trastuzumab therapy

Cardiac monitoring at baseline, 3, 6, and 9 mo

References available on page 170.

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities, individual patient variability, prior treatment, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

OTHER ADJUVANT REGIMENS

Docetaxel + trastuzumab followed by FEC chemotherapy[19]
• Docetaxel, 100 mg/m^2 by 1-h IV, day 1
Cycled every 21 days for 3 cycles
With
• Trastuzumab, 4 mg/kg IV, with first dose of docetaxel day 1
Followed by
• Trastuzumab, 2 mg/kg IV, weekly to complete 9 wk of trastuzumab
Followed by
• 5-Fluorouracil, 600 mg/m^2 IV, day 1
• Epirubicin, 60 mg/m^2, day 1
• Cyclophosphamide, 600 mg/m^2, day 1
Cycled every 21 days for 3 cycles
Cardiac monitoring at baseline, after last FEC cycle, at 12 and 36 mo after chemotherapy

Chemotherapy followed by trastuzumab[20]
• Approved adjuvant chemotherapy regimen for at least 4 cycles
Followed by
• Trastuzumab, 8 mg/kg IV, times 1 dose
Followed by
• Trastuzumab, 6 mg/kg IV, every 21 days for 1 y
Cardiac monitoring at baseline, 3, 6, and 9 mo

AC followed by docetaxel chemotherapy with trastuzumab[19]
• Doxorubicin, 60 mg/m^2 IV, day 1
• Cyclophosphamide, 600 mg/m^2, day 1
Cycled every 21 days for 4 cycles
Followed by
• Docetaxel, 100 mg/m^2
Cycled every 21 days for 4 cycles
With
• Trastuzumab, 4 mg/kg IV, wk 1
Followed by
• Trastuzumab, 2 mg/kg IV, weekly for 11 wk
Followed by
• Trastuzumab, 6 mg/kg, every 21 days to complete 1 y of trastuzumab therapy
Cardiac monitoring at baseline, 3, 6, and 9 mo

TRASTUZUMAB-CONTAINING COMBINATIONS

Neoadjuvant Regimens

Neoadjuvant T followed by FEC chemotherapy with trastuzumab[21]
• Trastuzumab, 4 mg/kg IV, for 1 dose beginning just before first dose of paclitaxel
Followed by
• Trastuzumab, 2 mg/kg IV, weekly for 23 wk
• Paclitaxel, 225 mg/m^2 by 24-h IV infusion every 21 days for 4 cycles(alternatively paclitaxel may be administered as paclitaxel, 80 mg/m^2 by 1-h IV infusion, weekly for 12 wk)
Followed by
• 5-Fluorouracil, 500 mg/m^2, days 1 and 4
• Epirubicin, 75 mg/m^2 IV, day 1
• Cyclophosphamide, 500 mg/m^2, day 1
Cycled every 21 days for 4 cycles

References available on page 170.

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities, individual patient variability, prior treatment, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

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DEFINITION OF MENOPAUSE

- Clinical trials in breast cancer have used various definitions of menopause. Menopause is generally the permanent cessation of menses and, as used in breast cancer management, includes a profound and permanent decrease in ovarian estrogen synthesis. Reasonable criteria for determining menopause include any of the following:
- Prior bilateral oophorectomy
- Age ≥ 60 y
- Age < 60 y and amenorrheic for ≥ 12 mo in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicular stimulating hormone (FSH) and estradiol in the postmenopausal range
- If taking tamoxifen or toremifene, and age < 60 y, then FSH and plasma estradiol level in postmenopausal ranges

It is not possible to assign menopausal status to women who are receiving an LH-RH agonist or antagonist. In women premenopausal at the beginning of adjuvant chemotherapy, amenorrhea is not a reliable indicator of menopausal status because ovarian function may still be intact or resume despite anovulation/amenorrhea after chemotherapy. For these women with therapy-induced amenorrhea, oophorectomy or serial measurement of FSH and/or estradiol are needed to ensure postmenopausal status if the use of aromatase inhibitors is considered a component of endocrine therapy.

SUBSEQUENT ENDOCRINE THERAPY FOR SYSTEMIC DISEASE (For first-line endocrine therapy, see page 151)

Premenopausal patients with ER-positive disease should have ovarian ablation/suppression and follow postmenopausal guideline

Postmenopausal patients:
- Nonsteroidal aromatase inhibitor (anastrozole, letrozole)
- Steroidal aromatase inactivator (exemestane)
- Fulvestrant
- Tamoxifen or toremifene
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol

PREFERRED CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER[1]

PREFERRED SINGLE AGENTS

Anthracyclines
- Doxorubicin
- Epirubicin
- Pegylated liposomal doxorubicin

Taxanes
- Paclitaxel
- Docetaxel
- Albumin-bound paclitaxel

Antimetabolites
- Capecitabine
- Gemcitabine

Other microtubule inhibitors
- Vinorelbine
- Eribulin

OTHER SINGLE AGENTS
- Cyclophosphamide
- Mitoxantrone
- Cisplatin
- Etoposide (po) (category 2B)
- Vinblastine
- Fluorouracil Cl
- Ixabepilone

PREFERRED AGENTS WITH BEVACIZUMAB[2]
- Paclitaxel

PREFERRED CHEMOTHERAPY COMBINATIONS
- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- AT (doxorubicin/docetaxel; doxorubicin/paclitaxel)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)

OTHER COMBINATIONS
- Ixabepilone + capecitabine (category 2B)

PREFERRED FIRST-LINE AGENTS FOR HER2-POSITIVE DISEASE

Trastuzumab with:
- Paclitaxel ± carboplatin
- Docetaxel
- Vinorelbine
- Capecitabine

PREFERRED AGENTS FOR TRASTUZUMAB-EXPOSED HER2-POSITIVE DISEASE
- Lapatinib + capecitabine
- Trastuzumab + other first-line agents
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)

[1]No compelling evidence shows that combination regimens are superior to sequential single agents.
[2]Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time to progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.

PREFERRED CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

PREFERRED CHEMOTHERAPY COMBINATIONS

CAF chemotherapy[1]
- Cyclophosphamide, 100 mg/m^2 PO, days 1-14
- Doxorubicin, 30 mg/m^2 IV, days 1 and 8
- 5-Fluorouracil, 500 mg/m^2 IV, days 1 and 8

Cycled every 28 days

FAC chemotherapy[2]
- 5-Fluorouracil, 500 mg/m^2 IV, days 1 and 8 or days 1 and 4
- Doxorubicin, 50 mg/m^2 IV, day 1
- Cyclophosphamide, 500 mg/m^2 IV, day 1

Cycled every 21 days

FEC chemotherapy[3]
- Cyclophosphamide, 400 mg/m^2 IV, days 1 and 8
- Epirubicin, 50 mg/m^2 IV, days 1 and 8
- 5-Fluorouracil, 500 mg/m^2 IV, days 1 and 8

Cycled every 28 days

AC chemotherapy[4]
- Doxorubicin, 60 mg/m^2 IV, day 1
- Cyclophosphamide, 600 mg/m^2 IV, day 1

Cycled every 21 days

EC chemotherapy[5]
- Epirubicin, 75 mg/m^2 IV, day 1
- Cyclophosphamide, 600 mg/m^2 IV, day 1

Cycled every 21 days

AT chemotherapy[6]
- Doxorubicin, 60 mg/m^2 IV, day 1
- Paclitaxel, 125-200 mg/m^2 IV, day 1

Cycled every 21 days

AT chemotherapy[7]
- Doxorubicin, 50 mg/m^2 IV, day 1
- Docetaxel, 75 mg/m^2 IV, day 1

Cycled every 21 days

CMF chemotherapy[8]
- Cyclophosphamide, 100 mg/m^2 PO, days 1-14
- Methotrexate, 40 mg/m^2 IV, days 1 and 8
- 5-Fluorouracil, 600 mg/m^2 IV, days 1 and 8

Cycled every 28 days

Docetaxel/capecitabine chemotherapy[9]
- Docetaxel, 75 mg/m^2 IV, day 1
- Capecitabine, 950 mg/m^2 PO, twice daily days 1-14

Cycled every 21 days

GT chemotherapy[10]
- Paclitaxel, 175 mg/m^2 IV, day 1
- Gemcitabine, 1250 mg/m^2 IV, days 1 and 8 (following paclitaxel on day 1)

Cycled every 21 days

OTHER COMBINATIONS

Ixabepilone/capecitabine (category 2B)
- Ixabepilone, 40 mg/m^2 IV, day 1
- Capecitabine, 2000 mg/m^2 PO, days 1-14

Cycled every 21 days

References available on pages 176 and 177.

The selection, dosing, and administration of ant-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities, individual patient variability, prior treatment, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

PREFERRED CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

PREFERRED SINGLE AGENTS

Anthracyclines:
Doxorubicin, 60-75 mg/m^2 IV, day 1[11]
Cycled every 21 days
OR
• Doxorubicin, 20 mg/m^2 IV, weekly[12]

• Epirubicin, 60-90 mg/m^2 IV, day 1[13]
Cycled every 21 days

• Pegylated liposomal encapsulated doxorubicin, 50 mg/m^2 IV, day 1[14]
Cycled every 28 days

Taxanes:
• Paclitaxel, 175 mg/m^2 IV, day 1[15]
Cycled every 21 days
OR
• Paclitaxel, 80 mg/m^2 IV, weekly[16]

• Docetaxel, 60-100 mg/m^2 IV, day 1[17,18]
Cycled every 21 days
OR
• Docetaxel, 40 mg/m^2 IV, weekly for 6 wk followed by a 2-wk rest, then repeat[19]

• Albumin-bound paclitaxel, 100 mg/m^2 or 150 mg/m^2, days 1, 8, and 15 IV[20,21]
Cycled every 28 days

Albumin-bound paclitaxel, 260 mg/m^2 IV[20]
Cycled every 21 days

Anti-metabolites:
• Capecitabine, 1000-1250 mg/m^2 PO, twice daily days 1-14[22]
Cycled every 21 days

• Gemcitabine, 800-1200 mg/m^2 IV, days 1, 8, and 15[23]
Cycled every 28 days

Other microtubule inhibitors:
• Vinorelbine, 25 mg/m^2 IV, weekly[24]
• Eribulin, 1.4 mg/m^2 IV, days 1 and 8
Cycled every 21 days

OTHER SINGLE AGENTS
• Cyclophosphamide
• Mitoxantrone
• Cisplatin
• Etoposide (PO) (category 2B)
• Vinblastine
• Fluorouracil CI
• Ixabepilone

PREFERRED AGENTS WITH BEVACIZUMAB

Paclitaxel plus bevacizumab[25]
• Paclitaxel, 90 mg/m^2 by 1-h IV, days 1, 8, and 15
• Bevacizumab, 10 mg/kg IV, days 1 and 15
Cycled every 28 days

References available on pages 176 and 177.

The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.

PREFERRED CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

PREFERRED FIRST-LINE AGENTS WITH TRASTUZUMAB FOR HER2-POSITIVE DISEASE

COMBINATIONS	SINGLE AGENTS	TRASTUZUMAB COMPONENT
PCH chemotherapy[26] • Carboplatin, AUC of 6 IV, day 1 • Paclitaxel, 175 mg/m^2 IV, day 1 Cycled every 21 days	• Paclitaxel, 175 mg/m^2 IV, day 1[28] Cycled every 21 days OR • Paclitaxel, 80-90 mg/m^2 IV, weekly[29]	Trastuzumab, 4 mg/kg IV, day 1 Followed by 2 mg/kg IV, weekly[28,37] OR Trastuzumab, 8 mg/kg IV, day 1 Followed by 6 mg/kg IV, every 3 wk[38]
Weekly TCH chemotherapy[27] • Paclitaxel, 80 mg/m^2 IV, days 1, 8, and 15 • Carboplatin, AUC of 2 IV, days 1, 8, and 15 Cycled every 28 days	• Docetaxel, 80-100 mg/m^2 IV, day 1[30] Cycled every 21 days OR • Docetaxel, 35 mg/m^2 IV, infusion weekly[31]	
	• Vinorelbine, 25 mg/m^2 IV, weekly[32]	
	• Capecitabine, 1000-1250 mg/m PO, twice daily days 1-14[33] Cycled every 21 days	

PREFERRED AGENTS FOR TRASTUZUMAB-EXPOSED HER2-POSITIVE DISEASE

	TRASTUZUMAB COMPONENT
Capecitabine plus lapatinib[34] • Capecitabine, 1000 mg/m^2 PO, twice daily days 1-14 • Lapatinib, 1250 mg PO, daily days 1-21 Cycled every 21 days	Trastuzumab, 4 mg/kg IV, day 1 Followed by 2 mg/kg IV, weekly[28,37] OR Trastuzumab, 8 mg/kg IV, day 1 Followed by 6 mg/kg IV, every 3 wk[38]
Trastuzumab + other first-line agents	
Trastuzumab + capecitabine[35]	
Trastuzumab + lapatinib[36] • Lapatinib, 1000 mg PO, daily	

References available on pages 176 and 177.

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities, individual patient variability, prior treatment, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

PREFERRED CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

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The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities, individual patient variability, prior treatment, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

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.

PREFERRED CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

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The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities, individual patient variability, prior treatment, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

Text continued from p. 137

NCCN Web site at www.NCCN.org). Women at increased risk for breast cancer (generally those with ≥ 1.67% 5-year risk of breast cancer using the Gail model of risk assessment[3]) may consider risk reduction strategies (see the NCCN Guidelines for Breast Cancer Risk Reduction; 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. Information on breast cancer staging can be found in the full breast cancer guidelines, available online at www.NCCN.org. Also available online and not published in this issue are sections of the guidelines on noninvasive breast cancer and special considerations in breast cancer.

Pathology Assessment

A central component of the treatment of breast cancer is full knowledge of disease extent and biologic features. These factors contribute to the determination of disease stage, assist in estimating the risk of cancer recurrence, and provide information that predicts response to therapy (e.g., hormone receptors, human epidermal growth factor receptor 2 [HER2]). These factors are determined by examination of excised tissue and provided in a written pathology report. Accurate pathology reporting requires communication between the clinician and pathologist regarding 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 (e.g., chemotherapy, radiation therapy). The specimens should be oriented for the pathologist, and specific requests for determination of biomarkers should be stated (e.g., estrogen receptor [ER], progesterone receptor [PR], 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.[5,6] Significant omissions include failure to orient and report surgical margins, and failure to report tumor grade consistently.

ER tumor status should be determined for all samples of ductal carcinoma in situ (DCIS), and ER and PR tumor status should be determined for all samples of invasive breast cancer. ER and PR tumor status is normally determined by immunohistochemistry testing. Although this method is considered reliable when performed by experienced pathology personnel, several reports have indicated that the reliability of ER and PR determinations can vary widely among laboratories.[7–9] These interlaboratory differences may be attributable to the diverse methodologies and diverse interpretation schema used to evaluate tumor hormonal status. An NCCN Task Force and a panel from ASCO and the College of American Pathologists (CAP) have reviewed this topic and issued recommendations on ER and PR testing in breast cancer.[10,11]

Along with ER and PR, the determination of HER2 tumor status for all newly diagnosed invasive breast cancers is specified in the NCCN Guidelines. HER2 status can be assessed by measuring the number of HER2 gene copies (fluorescence in situ hybridization [FISH]), or using a complementary method in which the quantity of HER2 cell surface receptors is assessed with immunohistochemistry.[12] Six methods currently have FDA approval for determining the HER2 status of breast cancer tumors: 1) IHC HercepTest (DAKO, Glostrup, Denmark)[13]; 2) IHC Pathway HER2 test (Ventana Medical Systems, Tucson, Arizona)[14]; 3) INFORM HER2 FISH test (Ventana Medical Systems)[15]; 4) PathVysion HER2 FISH test (Vysis, Downers Grove, Illinois)[16]; 5) the PharmaDX HER2 FISH test (DAKO),[17] and 6) SPOT-Light HER2 CISH test (Invitrogen, Carmarillo, California).[18] 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[19–23] and false-negative[19,24] HER2 test results are common. An NCCN Task Force reviewed this topic and is-

sued recommendations on HER2 testing in breast cancer,[25] which are summarized in the guideline (see page 159). The panel considers either immunohistochemistry or FISH acceptable for making an initial determination of HER2 tumor status provided that the test method has been 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 they demonstrate *HER2* gene amplification using a FISH method or are scored as 3+ with an immunohistochemistry method. 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 2+ scores using immunohistochemistry) are described in the guideline (see page 159). Only accredited laboratories should perform HER2 testing. Furthermore, these laboratories should have established standardized HER2 testing procedures, and programs to periodically evaluate the proficiency of personnel performing HER2 testing. Some of the information that HER2 test reports must provide include information on tumor site, specimen type, histologic type, fixation method and time, block examined, and details on the HER2 testing methods used. Clinicians should be familiar with the significance of these criteria when making clinical recommendations for individual patients.

A joint panel from ASCO and 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.[26] The panel endorses CAP accreditation for anatomic pathology laboratories performing HER2 testing.

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

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

Treatment Approach

Conceptually, breast cancer involves 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 treatment should be similar to that for postmenopausal women, except that aromatase inhibitors are ineffective without concomitant suppression of testicular steroidogenesis.[27,28] Patient preference is a major component of the decision-making process, especially when survival rates are equivalent among the available treatment options.

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). Information on the pure noninvasive carcinomas can be found in the full breast cancer guidelines, available online at www.NCCN.org.

Stage I, IIA, IIB, or T3N1M0 Invasive Breast Cancer

The recommended workup and staging of invasive breast cancer includes history and physical examination, a complete blood cell count, platelet count, liver function tests, bilateral diagnostic mammography, breast ultrasonography if necessary, tumor ER and PR determinations, HER2 tumor status determination, and pathology review (see page 138). Genetic counseling is recommended if the patient is

considered to be at high risk of 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 the NCCN Web site at www.NCCN.org).

MRI is optional in the evaluation of women considering breast-conserving therapy. MRI of the breast should be performed using a dedicated breast coil, in consultation with the multidisciplinary treatment team, and by a breast imaging team capable of performing MRI-guided biopsy (see page 160). Limitations of breast MRI include a high percentage of false-positive findings.[29–31] MRI imaging of the breast, therefore, should generally be considered for staging breast cancer in patients whose breasts cannot be imaged adequately with mammography and ultrasound (e.g., women with very dense breast tissue; women with positive axillary nodal status and occult primary tumor presumed to originate in the breast; to evaluate the chest wall).[32]

No randomized, prospective assessment is available regarding the efficacy of MRI in staging of or deciding treatment for breast cancer. One retrospective study suggested an outcome benefit,[33] whereas another did not.[34] One systematic review[31] documented breast MRI staging to alter surgical treatment in 7.8% to 33.3% of women. However, no differences in outcome, if any, can be shown in that analysis. Patients should not be denied the option of breast-conservation therapy based on MRI findings alone in the absence of tissue sampling.

For patients with clinical stage T3N1M0 disease, additional staging studies should be considered, including bone scan (category 2B), abdominal imaging using CT, ultrasound, or MRI, and chest imaging. These studies are not indicated in patients with stage I disease with no signs or symptoms of metastatic disease, nor are they needed in many other patients with early-stage breast cancer.[35] For patients with stage I, stage II, or T3N1M0 disease, radionuclide bone scanning; abdominal imaging with CT, ultrasound, or MRI; and chest imaging are typically indicated only for those with signs or symptoms related to the bone, abdomen, or chest (e.g., pain, abnormal laboratory tests, pulmonary symptoms). These recommendations are supported by a study evaluating patients with newly diagnosed breast cancer using bone scan, liver ultrasonography, and chest radiography.[36] Metastases were identified by bone scan in 5.1%, 5.6%, and 14% of patients with stage I, II, and III disease, respectively, whereas liver ultrasonography or chest radiography detected no evidence of metastasis in patients with stage I or II disease.

The panel recommends against using PET or PET/CT scan in staging these patients. The recommendation against the use of PET scanning is supported by the high false-negative rate in the detection of lesions that are small (< 1 cm) and/or low grade, low sensitivity for detecting axillary nodal metastases, low prior probability of these patients having detectable metastatic disease, and high rate of false-positive scans.[37–42]

Fertility

Numerous epidemiologic studies have shown that childbearing after treatment of invasive breast cancer does not increase rates of breast cancer recurrence or death.[43] The offspring of pregnancies that occur after treatment do not have an increased rate of birth defects or other serious childhood illness. However, treatment for breast cancer, especially with cytotoxic agents, may impair fertility. Therefore, considering fertility preservation before breast cancer treatment in young women who wish to bear children after breast cancer therapy is reasonable and appropriate.[44–46]

No high-level evidence shows that ovarian suppression or other interventions decrease the toxicity of cytotoxic chemotherapy on the premenopausal ovary.[47] However, many women, especially those younger than 35 years, regain menstrual function within 2 years of completing chemotherapy.[48] Resumption of menses does not necessarily correlate with fertility, and fertility may be preserved in the absence of menses. Should a premenopausal woman with newly diagnosed nonmetastatic breast cancer desire to bear children after treatment, she should consult with a physician who has expertise in fertility. Multiple factors should be considered when deciding on fertility preservation, including age, risk of premature ovarian failure based on anticipated chemotherapy, and length of optimal endocrine therapy. To ensure fetal safety, women must not become pregnant during breast cancer treatment (see page 160).

Locoregional Treatment

Several randomized trials document that mastectomy with axillary lymph node dissection is equivalent to breast-conserving therapy with lumpectomy, axil-

lary dissection, and whole breast irradiation as primary breast treatment for most women with stage I and II breast cancers (category 1).[49–52]

The panel recommends whole breast irradiation include most of the breast tissue, and should be performed after CT-based treatment planning to limit irradiation exposure of the heart and lungs, and to assure adequate coverage of the primary tumor and surgical site. Tissue wedging, forward planning with segments (step and shoot), or intensity-modulated radiation therapy (IMRT) is recommended.[53] Dose/fraction schedules of either 50 Gy in 25 fractions over 35 days or 42.5 Gy in 16 fractions over 22 days have been prospectively evaluated and showed comparable disease-free and overall survivals in a study of women with node-negative early-stage breast cancer with a median follow-up of 69 months.[54]

Randomized trials have shown a decrease in in-breast recurrences with an additional "boost" dose of radiation (by photons, brachytherapy, or electron beam) to the tumor bed.[55,56] The relative reduction in risk of local recurrence with the addition of a boost is similar across age groups (from ≤ 40 to > 60 years of age), although the absolute gain in local control is highest in younger patients. There is a demonstrated benefit favoring a boost in patients with positive axillary nodes, lymphovascular invasion, or close margins (see page 164). For example, a subset analysis from an EORTC trial involving only patients for whom central pathology review of tumor margins was available (1724 of 5318 total patients) showed that the 10-year relapse rate was significantly lower when women with positive tumor margins received a boost (4% vs. 13%; $P = .0001$). However, a boost did not significantly lower the relapse rate in the group with negative margins.[57] Hence, the panel recommends a boost be considered after postlumpectomy whole breast irradiation (see page 139).

Administration of whole breast irradiation therapy with or without a boost to the tumor bed after lumpectomy is a category 1 recommendation for patients with node-positive disease (category 2A recommendation for those with node-negative disease). These NCCN Guidelines include a recommendation for regional lymph node irradiation in patients treated with breast-conserving surgery (see page 139) in situations analogous to those recommended for patients treated with postmastectomy irradiation (see pages 140 and 164). Radiation therapy to the infraclavicular region and supraclavicular area is recommended for patients with 4 or more positive lymph nodes (category 2A), and should be strongly considered in those with 1 to 3 positive lymph nodes (category 2B). Although data are not yet available from ongoing randomized clinical trials evaluating regional lymph node irradiation in patients with node-positive disease treated with breast-conserving surgery, extrapolation of results of studies of patients undergoing mastectomy is supported by similarities in tumor biology. In addition, consideration should be given to irradiation of the internal mammary nodes (category 3; see Radiation Therapy After Mastectomy, page 139, and see page 164).

The use of breast-conserving therapy is absolutely contraindicated for patients who have received previous moderate- or high-dose radiation to the breast or chest wall, are pregnant and would require radiation during pregnancy, have diffuse suspicious or malignant-appearing microcalcifications on mammography, have widespread disease that cannot be incorporated by local excision through a single incision with a satisfactory cosmetic result, or have positive pathologic margins (see page 162). Patients with a pathologically positive margin should generally undergo reexcisions to achieve a negative pathologic margin. If the margins remain positive after reexcisions, then mastectomy may be required for optimal local disease control. To adequately assess margins after lumpectomy, the panel recommends that the surgical specimens be oriented and that the pathologist provide descriptions of the gross and microscopic margin status, and the distance, orientation, and type of tumor (invasive or DCIS) in relation to the closest margin.

Relative contraindications to breast-conserving therapy include active connective tissue disease involving the skin (especially scleroderma and lupus), tumors larger than 5 cm (category 2B), and focally positive pathologic margins (see page 162). Patients with focally positive pathologic margins who do not undergo reexcision should be considered for a higher radiation boost dose to the tumor bed.

Several studies of women with early-stage breast cancer treated with breast-conserving therapy have identified young age as a significant predictor of an increased likelihood of ipsilateral breast tumor recurrence after breast-conserving surgery.[58–61] Young women who have breast cancer are more likely to have risk

factors, such as a family history of breast cancer or a genetic predisposition for breast cancer (e.g., *BRCA 1/2* or other mutation), thereby confounding the independent contributions of age and treatment to clinical outcome.[62] Survival outcomes are similar among young women with breast cancer undergoing either breast-conserving therapy or mastectomy.[63]

Several studies have been reported using accelerated partial breast irradiation (APBI) rather than whole breast irradiation after complete surgical excision of in-breast disease. The panel generally considers APBI investigational, and encourages its use within the confines of a high-quality prospective clinical trial.[64] For patients who are not eligible for a clinical trial, recommendations from the American Society for Radiation Oncology (ASTRO) indicate that APBI may be suitable in selected patients with early-stage breast cancer and may be comparable to treatment with standard whole breast radiation therapy.[65] Patients who may be suitable for APBI are women aged 60 years and older who are not carriers of a known *BRCA1/2* mutation and have been treated with primary surgery for a unifocal stage I, ER-positive cancer. Tumors should be infiltrating ductal or have a favorable histology, should not be associated with an extensive intraductal component or LCIS, and margins should be negative. A regimen involving 34 Gy in 10 fractions delivered twice daily with brachytherapy, or 38.5 Gy in 10 fractions delivered twice daily with external-beam photon therapy to the tumor bed, is recommended. Other fractionation schemes are under investigation.

Ongoing studies have suggested that the ASTRO stratification guidelines may not adequately predict ipsilateral breast tumor recurrence (IBTR) after APBI.[66,67] Follow-up is limited and studies are ongoing.

Only limited data are available on the survival impact of mastectomy contralateral to a unilateral breast cancer.[68] A recent analysis of women included in the SEER database who were treated with mastectomy for a unilateral breast cancer during 1998 to 2002 showed that contralateral mastectomy performed at treatment of a unilateral cancer was associated with a reduction in breast cancer–specific mortality only in young women (18–49 years of age) with stage I/II, ER-negative breast cancer (hazard ratio [HR], 0.64; 95% CI, 0.44–0.94; $P = .025$).[69] The panel recommends that women with breast cancer who are aged 35 years or younger or premenopausal, and those who are carriers of a known *BRCA1/2* mutation, consider additional risk reduction strategies after appropriate risk assessment and counseling (see page 162, and the NCCN Guidelines for Breast Cancer Risk Reduction and 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). This process should involve multidisciplinary consultations before surgery, and include a discussion of the risks associated with development of a contralateral breast cancer compared with the risks associated with recurrent disease from the primary cancer. Except as specifically outlined in these NCCN Guidelines, the panel discourages prophylactic mastectomy of a breast contralateral to a known unilateral breast cancer treated with mastectomy. The use of a prophylactic mastectomy contralateral to a breast treated with breast-conserving surgery is very strongly discouraged in all patients.

Whole breast irradiation as a component of breast-conserving therapy is not always necessary in selected women aged 70 years or older. In one study, women with clinical stage I, ER-positive breast cancer aged 70 years or older at diagnosis were randomized to undergo lumpectomy with whole breast radiation or lumpectomy alone, both with tamoxifen for 5 years. Locoregional recurrence rates were 1% in the lumpectomy, radiation, and tamoxifen arm, and 4% in the lumpectomy plus tamoxifen arm. No differences were seen in overall or disease-free survival, or need for mastectomy.[70] These results were confirmed in an updated analysis of this study with a median follow-up of 10.5 years.[71]

Similar results were obtained in another study of similar design.[72] These guidelines allow for the use of breast-conserving surgery (pathologically negative margin required) plus tamoxifen or an aromatase inhibitor without breast irradiation in women aged 70 or older with clinically negative lymph nodes and ER-positive, T1 breast cancer (category 1 with tamoxifen; category 2A with an aromatase inhibitor).

If adjuvant chemotherapy is indicated after breast-conserving surgery, radiation should be given after chemotherapy is completed.[73,74] This recommendation is based partly on results of the "Up-front–Outback" trial in which patients who had undergone breast-conserving surgery and axillary

dissection were randomly assigned to undergo either chemotherapy after radiation therapy or radiation therapy after chemotherapy. An increased rate of distant recurrence was seen in the group who had delayed radiation therapy at a median follow-up of 58 months, although differences in distant or local recurrence rates were not significant when the arms were compared at 135 months follow-up.[73,74]

These guidelines include a guideline for surgical staging of the axilla for stages I, IIA, and IIB breast cancer (see page 161). A typical woman with clinical stage I or II breast cancer requires pathologic assessment of the axillary lymph node status.

The panel recommends sentinel lymph node mapping and resection in the surgical staging of the clinically negative axilla to assess the pathologic status of the axillary lymph nodes in patients with clinical stage I or II breast cancer[75–84] (category 1; see page 161). This recommendation is supported by results of recent randomized clinical trials showing decreased arm and shoulder morbidity (e.g., pain, lymphedema, sensory loss) in patients with breast cancer undergoing sentinel lymph node biopsy compared with those undergoing standard axillary node dissection.[84,85] These studies showed no significant differences in effectiveness between the SLN procedure or level I and II dissection for determining the presence or absence of metastases in axillary nodes. However, not all women are candidates for sentinel lymph node resection.

The availability of an experienced sentinel lymph node team is mandatory for the use of sentinel lymph node mapping and excision.[86,87] Women who have clinical stage I or II disease and do not have immediate access to an experienced sentinel lymph node team should be referred to one for the definitive surgical treatment of the breast and surgical axillary lymph node staging. In addition, potential candidates for sentinel lymph node mapping and excision should have clinically negative axillary lymph nodes or a negative core or fine needle aspiration (FNA) biopsy of any clinically suspicious axillary lymph nodes. If the sentinel lymph node cannot be identified or is positive for metastasis, a formal axillary lymph node dissection should be performed (category 2A) or axillary irradiation administered (category 2B).

The optimal technique for axillary radiation is not established in studies, but the axillary nodes can be included in the breast tangential fields. If lymph node mapping identifies sentinel lymph nodes in the internal mammary chain, internal mammary node excision is considered optional (category 3). Many institutions use both hematoxylin and eosin (H&E) staining and cytokeratin immunohistochemistry to assess sentinel lymph nodes for the presence of metastases. The clinical significance of a lymph node that is negative on H&E staining but positive on cytokeratin immunohistochemistry is unclear. Because the historical and clinical trial data on which treatment decisions are based rely on H&E staining, the panel does not recommend routine cytokeratin immunohistochemistry to define node involvement and believes that current treatment decisions should be made based solely on H&E staining. This recommendation is further supported by a recently reported randomized clinical trial for patients with H&E-negative nodes, in which further examination using cytokeratin immunohistochemistry did not lead to significantly improved overall survival at 5 years.[88] In the uncommon situation in which H&E staining is equivocal, relying on the results of cytokeratin immunohistochemistry is appropriate.

Multiple attempts have been made to identify cohorts of women with involved sentinel lymph nodes who have a low enough risk for non–sentinel lymph node involvement that a complete axillary dissection might be avoided if the sentinel lymph node is positive. Unfortunately, none can identify a group of patients with positive sentinel lymph node biopsies with low enough risk to eliminate the need for ALND.[89–95] A randomized trial compared sentinel lymph node resection alone and ALND in women aged 18 and older with T1/T2 tumors and fewer than 3 positive sentinel lymph nodes who were undergoing breast-conserving surgery and whole breast irradiation. In this study, no difference in local recurrence, disease-free survival, or overall survival were seen. Only ER-negative status, age younger than 50 years, and lack of adjuvant systemic therapy were associated with decreased overall survival.[96,97]

Level I or II axillary dissection is the recommended staging study in women with stage III breast cancer. In addition, ALND remains indicated in women found to have axillary lymph node involvement on sentinel lymph node excision. Traditional level I and II axillary dissection required that at least 10 lymph nodes be provided for pathologic evaluation to accu-

rately stage the axilla.[98,99] Axillary dissection should be extended to include level III nodes only if gross disease is apparent in the level I or II nodes.

Furthermore, in the absence of definitive data showing superior survival with ALND or sentinel lymph node resection, these procedures may be considered optional in patients who have particularly favorable tumors, for whom the selection of adjuvant systemic therapy is unlikely to be affected by the results of the procedure, who are elderly, and who have serious comorbid conditions (see page 160). Women who do not undergo axillary dissection or axillary lymph node irradiation are at increased risk for ipsilateral lymph node recurrence.[100] Women who undergo mastectomy are appropriate candidates for breast reconstruction.

Preoperative Chemotherapy for Large Clinical Stage IIA and IIB Tumors and T3N1M0 Tumors

Preoperative chemotherapy should be considered for women with large clinical stage IIA, stage IIB, and T3N1M0 tumors who meet the criteria for breast-conserving therapy except for tumor size, and who wish to undergo breast-conserving therapy. In the available clinical trials of preoperative chemotherapy, pretreatment biopsies have been limited to core needle biopsy or FNA cytology. Therefore, in patients anticipated to undergo preoperative chemotherapy, core biopsy of the breast tumor and localization of the tumor bed for future surgical management should be performed. For patients with clinically negative axillary nodes, sentinel lymph node biopsy can be considered. For those with clinically suspicious axillary lymph nodes, the panel recommends consideration of either a core biopsy or FNA of these nodes, along with a sentinel node biopsy if FNA or core biopsy results are negative.[101] Preoperative chemotherapy is not indicated unless invasive breast cancer is confirmed. Recommended staging studies are outlined on page 147.

The current NCCN Guidelines list prechemotherapy sentinel lymph node resection as the preferred option for surgical axillary staging for women with clinically negative ipsilateral axillary examinations (see page 161). If the sentinel lymph node is histologically negative, omission of the axillary dissection may be considered at the time of local surgical therapy. If the sentinel lymph node is histologically positive, then level I and II axillary dissection should be performed at the time of definitive surgical therapy. If a prechemotherapy sentinel lymph node excision is not performed, then a level I and II axillary dissection (category 2A) or sentinel lymph node excision (category 3; with level I and II axillary dissection if the sentinel lymph node is positive) should be performed at the time of definitive surgical therapy. The false-negative rate of sentinel lymph node biopsy in the pre- and postchemotherapy settings is low.[80,102,103]

Nevertheless, the possibility remains that a pathologic complete response after chemotherapy may occur in lymph node metastases previously undetected during clinical examination. Therefore, the panel generally recommends a prechemotherapy sentinel lymph node excision because it provides additional information to guide local and systemic treatment decisions. If sentinel lymph node resection is performed after administration of preoperative chemotherapy, both the prechemotherapy clinical and the postchemotherapy pathologic nodal stages must be used to determine the risk of local recurrence. Close communication between members of the multidisciplinary team, including the pathologist, is particularly important when any treatment strategy involving preoperative chemotherapy is planned.

In some patients, preoperative chemotherapy results in tumor response sufficient enough that breast-conserving therapy becomes possible. Because complete or near-complete clinical responses are common, percutaneously placing clips into the breast under mammographic or ultrasound guidance, or another method of localizing prechemotherapy tumor volume, aids in the postchemotherapy resection of the original area of tumor and is encouraged. Results of the NSABP B-18 trial show that breast conservation rates are higher after preoperative chemotherapy.[104] However, preoperative chemotherapy has no demonstrated disease-specific survival advantage over postoperative adjuvant chemotherapy in patients with stage II tumors.

NSABP B-27 is a 3-arm, randomized phase III trial of 2411 women with invasive breast cancer treated with preoperative doxorubicin and cyclophosphamide (AC) chemotherapy for 4 cycles followed by local therapy alone, preoperative AC followed by preoperative docetaxel for 4 cycles followed by local therapy, or AC followed by local therapy followed by 4 cycles of postoperative docetaxel. Results from this study documented a higher rate of complete pathologic response

at the time of local therapy in patients treated preoperatively with 4 cycles of AC followed by 4 cycles of docetaxel versus 4 cycles of preoperative AC. Results did not show disease-free and overall survival to be superior after docetaxel treatment.[105] However, a disease-free survival advantage was seen (HR, 0.71; 95% CI, 0.55–0.91; P = .007) that favored preoperative versus postoperative docetaxel in the subset of patients experiencing a clinical partial response to AC.

Several chemotherapy regimens have been studied as preoperative chemotherapy in the neoadjuvant setting. The panel believes that the regimens recommended in the adjuvant setting (see pages 166–170) are appropriate to consider in the preoperative chemotherapy setting. The benefits of "tailoring" preoperative chemotherapy (i.e., switching after limited response) or using preoperative chemotherapy to evaluate disease responsiveness have not been well studied.[106] In women with HER2-positive tumors treated with neoadjuvant chemotherapy, the addition of neoadjuvant trastuzumab to paclitaxel followed by FEC chemotherapy (fluorouracil, epirubicin, and cyclophosphamide) was associated with an increase in the pathologic complete response rate from 26% to 65.2% (P = .016).[107] Thus, the incorporation of trastuzumab into neoadjuvant chemotherapy regimens seems important in HER2-positive tumors.[108]

Several randomized trials have assessed the value of neoadjuvant endocrine therapy in postmenopausal women with ER-positive breast cancer. These studies have generally compared the rates of objective response and of breast-conserving surgery among patients undergoing treatment with tamoxifen, anastrozole, anastrozole plus tamoxifen, or letrozole. These studies consistently show that the use of either anastrozole or letrozole alone provides superior rates of breast-conserving surgery and usually objective response when compared with tamoxifen.[109,110] Based on these trials, if preoperative endocrine therapy is to be used, an aromatase inhibitor is preferred in the treatment of postmenopausal women with hormone receptor–positive disease.

If the tumor responds to preoperative chemotherapy, lumpectomy plus (if prechemotherapy sentinel lymph node staging was not done or was positive) axillary lymph node dissection (category 2A) or (if prechemotherapy axillary lymph node staging not performed) sentinel lymph node procedure (category 3) may be considered if the requirements for breast-conserving therapy are fulfilled (see pages 148 and 149). If a prechemotherapy sentinel lymph node procedure was performed and the sentinel lymph node was pathologically negative, then further axillary lymph node staging is not necessary. If a prechemotherapy sentinel lymph node procedure was performed and it was positive, then a level I/II axillary lymph node dissection should be performed. Surgery should be followed by individualized chemotherapy, such as taxanes (category 2B), if the full course of planned chemotherapy was not administered preoperatively, and breast and regional lymph node irradiation. Panel consensus is that postoperative chemotherapy has no role if a full course of standard chemotherapy was completed preoperatively. If after several cycles of preoperative chemotherapy the tumor fails to respond, the response is minimal, or the disease progresses at any point, an alternative chemotherapy should be considered followed by local therapy, usually a mastectomy plus axillary dissection, with or without breast reconstruction.

Postoperative treatment for these patients consists of individualized chemotherapy, and endocrine therapy after chemotherapy in women with ER- and/or PR-positive tumors. Up to 1 year of trastuzumab therapy should be completed for HER2-positive tumors (category 1). Radiation should be delivered to the chest wall and supraclavicular lymph nodes (see page 164). Including the internal mammary lymph nodes in the radiation field can be considered, but this recommendation generated substantial controversy among panel members (category 3). Postmastectomy radiation therapy in patients with T2N0M0 tumors may be considered optional. Endocrine therapy and trastuzumab can be administered concurrently with radiation therapy if indicated.

Radiation Therapy After Mastectomy

Node-Positive Disease: Three randomized clinical trials have shown that disease-free and overall survival advantages are conferred by the addition of chest wall and regional lymph node irradiation in women with positive axillary lymph nodes after mastectomy and axillary lymph node dissection.[111–115] In these trials, the ipsilateral chest wall and ipsilateral locoregional lymph nodes were irradiated. On the basis of these studies, the current guidelines call for postmastectomy irradiation in women with 4 or more positive axillary lymph nodes and strong con-

sideration of postmastectomy irradiation in women with 1 to 3 positive axillary lymph nodes. Two retrospective analyses have provided evidence for benefit of radiation therapy for only selected patients undergoing preoperative chemotherapy before mastectomy.[116,117] However, the panel recommends that decisions related to the administration of radiation therapy for patients undergoing neoadjuvant chemotherapy be made based on prechemotherapy tumor characteristics, irrespective of tumor response to preoperative chemotherapy (i.e., radiation therapy is recommended in patients with clinical stage III disease and a pathologic complete response to neoadjuvant chemotherapy).

Women with 4 or more positive axillary lymph nodes are at substantially increased risk for locoregional recurrence of disease. The use of prophylactic chest wall irradiation in this setting substantially reduces the risk of local recurrence.[50] The use of postmastectomy, postchemotherapy chest wall, and regional lymph node irradiation is recommended (category 1).

The recommendation for strong consideration of chest wall and supraclavicular irradiation in women with 1 to 3 involved axillary lymph nodes (see page 140) generated substantial controversy among panel members. The use of regional nodal irradiation is supported by a subgroup analysis of studies from the Danish Breast Cancer Collaborative Group.[118] In this analysis, a substantial survival benefit was associated with postmastectomy radiation therapy for women with 1 to 3 positive axillary lymph nodes. Some panel members believe chest wall and supraclavicular irradiation should be used routinely after mastectomy and chemotherapy in this subgroup of patients. However, other panel members believe radiation should be considered in this setting but should not be mandatory, given the studies that do not show an advantage. This is an unusual situation in which high-level evidence exists but is contradictory.[50,113–115,118] Women with 1 to 3 involved axillary lymph nodes and tumors greater than 5 cm or tumors with pathologic margins postmastectomy should undergo radiation therapy to the chest wall and supraclavicular area.

The panel also recommends consideration of ipsilateral internal mammary field radiation therapy in women with positive axillary lymph nodes (category 3). However, considerable disagreement exists regarding the inclusion of the ipsilateral internal mammary field. Some panel members believe that irradiation of the internal mammary nodes is unnecessary and produces possible morbidity. Internal mammary node radiation has not been isolated as an independent factor in decreasing recurrence. Others believe internal mammary nodes should be included in the radiation fields, as used in studies showing an advantage for postmastectomy, postchemotherapy radiation therapy. Panel consensus is that radiation therapy should be administered to clinically or pathologically positive ipsilateral internal mammary lymph nodes; otherwise, treatment of the internal mammary lymph nodes is at the discretion of the treating radiation oncologist.

Postmastectomy irradiation should be performed using CT-based treatment planning to assure reduced radiation dose to the heart and lungs. The recommended radiation is 50 Gy in fractions of 1.8 to 2.0 Gy to the ipsilateral chest wall, mastectomy scar, and drain sites. Additional boost dose of radiation to the mastectomy scar can be delivered (e.g., 2 Gy fractionated in 5 doses, typically with electrons). Radiation dose to regional lymph nodes is 50 Gy given in fractions of 1.8 to 2.0 Gy.

Node-Negative Disease: Features in node-negative tumors that predict a high rate of local recurrence include primary tumors greater than 5 cm and close (< 1 mm) or positive pathologic margins. Chest wall irradiation is recommended for these patients.[119] Radiation to the ipsilateral supraclavicular area and the ipsilateral internal mammary lymph nodes should be considered (category 3), especially in patients with inadequate axillary evaluation or extensive lymphovascular invasion. Postmastectomy radiation therapy is not recommended for patients with negative margins, tumors 5 cm or smaller, and no positive axillary lymph nodes.

The panel recommends that decisions related to administration of radiation therapy for patients undergoing preoperative chemotherapy should be made based on prechemotherapy tumor characteristics irrespective of response to neoadjuvant chemotherapy.

Breast Reconstruction

Breast Reconstruction After Mastectomy: Mastectomy results in loss of the breast for breastfeeding, loss of sensation in the skin of the breast and nipple–areolar complex (NAC), and loss of the breast for cosmetic, body image, and psychosocial purposes. The loss of the

breast for cosmetic, body image, and psychosocial issues may be partially overcome through breast reconstruction with or without reconstruction of the NAC. Reconstruction can be performed either immediately after mastectomy and under the same anesthetic or in a delayed fashion after mastectomy.

Several factors must be considered in the decision-making about breast reconstruction after mastectomy (see page 163). Several different types of breast reconstruction are available, including those that use implants, autogenous tissues, or both.[120] Reconstruction with implants can be performed through either immediate placement of a permanent subpectoral implant or initial placement of a subpectoral expander implant followed by gradual expansion of the implant envelope with stretching of the pectoralis major muscle and overlying skin, followed by replacement of the expander with a permanent implant.

A wide variety of implants are available that contain saline, silicone gel, or a combination of saline and silicone gel inside a solid silicone envelope. Autogenous tissue methods of reconstruction use various combinations of fat, muscle, skin, and vasculature from donor sites (e.g., abdomen, buttock, back) that may be brought to the chest wall with their original blood supply (pedicle flap) or as free flaps with microvascular anastomoses to blood supply from the chest wall/thorax. Several procedures using autologous tissue are available, including trans rectus abdominis myocutaneous (TRAM) flap, latissimus dorsi flap, and gluteus myocutaneous flap reconstruction. Composite reconstruction techniques use implants in combination with autogenous tissue reconstruction to provide volume and symmetry. Patients with underlying diabetes or who smoke tobacco have increased rates of complications after autogenous tissue breast cancer reconstruction, presumably because of underlying microvascular disease.

Skin-sparing mastectomy procedures are appropriate for some patients and involve removal of the breast parenchyma, including the NAC while preserving most of the original skin envelope and followed by immediate reconstruction with autogenous tissue, a prosthetic implant, or a composite of autogenous tissue and an implant. Advantages of skin-sparing procedure include an improved cosmetic outcome resulting in a smaller mastectomy scar and more natural breast shape, especially when autologous tissue is used in reconstruction,[121] and the ability to perform immediate reconstruction. Although no randomized studies have been performed, results of several mostly retrospective studies have indicated that patients undergoing skin-sparing mastectomies do not have increased risk of local recurrence compared with those undergoing non–skin-sparing procedures, although strong selection biases almost certainly exist in the identification of patients appropriate for skin-sparing procedures.[122–126] Reconstruction of the NAC may also be performed in a delayed fashion if the patient desires. Reconstructed nipples are devoid of sensation.

Plans for postmastectomy radiation therapy can impact decisions related to breast reconstruction because there is a significantly increased risk of implant capsular contracture after irradiation of an implant. Furthermore, postmastectomy irradiation may have a negative impact on breast cosmesis when autologous tissue is used in immediate breast reconstruction, and may interfere with the targeted delivery of radiation when immediate reconstruction is performed using either autologous tissue or breast implants.[127,128] Some studies, however, have not shown a significant compromise in reconstruction cosmesis after irradiation.[129] Although the panel generally recommends delayed reconstruction for patients who will undergo postmastectomy radiation therapy, the preferred reconstruction approach was a subject of controversy among the panel, and several approaches are summarized on page 163.

The decision regarding type of reconstruction includes patient preference, body habitus, smoking history, comorbidities, plans for irradiation, and expertise and experience of the reconstruction team. Reconstruction is an optional procedure that does not impact the probability of recurrence or death, but is associated with an improved quality of life for many patients. Sometimes surgery must be performed on the contralateral breast (e.g., breast reduction, implantation) to achieve optimal symmetry between it and the ipsilateral reconstructed breast.

Recently, skin-sparing mastectomy involving preservation of the skin of the NAC has become the subject of increased attention. Possible advantages of this procedure include improvements in breast cosmesis, body image, and nipple sensation after mastectomy, although the impact of this procedure on these quality-of-life issues has not been well studied.[130–132] Limited data from recent surgical series

with relatively short follow-up suggest that performance of NAC-sparing mastectomy in selected patients is associated with low rates of both occult involvement of the NAC with breast cancer and local recurrence of disease.[131,133,134] Nevertheless, the panel recommends that mastectomy in the setting of breast cancer involve removal of the NAC (see page 163) because long-term follow-up is not available and selection criteria for appropriate candidates have not been defined. Several prospective trials are evaluating NAC-sparing mastectomy in the setting of cancer, and enrollment in these trials is encouraged.

Because breast reconstruction does not impact disease recurrence or survival, the expectations and desires of the patient are paramount in the decision-making process. When breast reconstruction after mastectomy is planned, close prospective evaluation and collaboration among members of the breast cancer treatment team is essential, including the oncologic and reconstructive surgeons, other members of the multidisciplinary breast cancer team, and the patient.

Breast Reconstruction After Breast-Conserving Surgery: Issues related to breast reconstruction also pertain to women who undergo or have undergone a lumpectomy, particularly when the surgical defect is large and/or expected to be cosmetically unsatisfactory. The evolving field of oncoplastic surgery includes the use of "volume displacement" techniques performed in conjunction with a large partial mastectomy.[135] Oncoplastic volume displacement procedures combine the removal of generous regions of breast tissue (typically designed to conform to the segmentally distributed cancer in the breast) with mastopexy techniques, in which remaining breast tissues are shifted together within the breast envelope to fill the resulting surgical defect and thereby avoid the creation of significant breast deformity. Volume displacement techniques are generally performed during the same operative setting as the breast-conserving lumpectomy by the same surgeon who is performing the cancer resection.[136,137]

Advantages of oncoplastic volume displacement techniques are that they permit the removal of larger regions of breast tissue, thereby achieving wider surgical margins around the cancer, and preserve the natural shape and appearance of the breast better than standard breast resections.[138] Limitations of oncoplastic volume displacement techniques include lack of standardization among centers, performance at only a limited number of sites in the United States, and the possible necessity for subsequent mastectomy if pathologic margins are positive when further breast-conserving attempts are deemed impractical or unrealistic. Nevertheless, panel consensus is that these issues should be considered before surgery for women who are likely to have a surgical defect that is cosmetically unsatisfactory, and that women who undergo lumpectomy and are dissatisfied with the cosmetic outcome after treatment should be offered a consultation with a plastic surgeon to address the repair of resulting breast defects. Finally, the primary focus should be on treatment of the tumor, and this treatment should not be compromised when decisions regarding breast reconstruction are made.

Systemic Adjuvant Therapy

After surgical treatment, adjuvant systemic therapy should be considered. The published results of the Early Breast Cancer Trialists' Collaborative Group overview analyses of adjuvant polychemotherapy and tamoxifen show convincing reductions in the odds of recurrence and death in all age groups younger than 70 years for polychemotherapy, and in all age groups for tamoxifen.[2] Thus, for patients younger than 70 years, the current NCCN Guidelines recommend adjuvant therapy without regard to patient age (category 1). When deciding to use systemic adjuvant therapy, risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of the therapy, and comorbidity must be considered and balanced.[139,140] The decision-making process requires collaboration among the health care team and patient.

Panel consensus is that data are insufficient to make definitive chemotherapy recommendations for patients older than 70 years. Although AC with cyclophosphamide, methotrexate and fluorouracil (CMF) was found to be superior to capecitabine in a randomized trial of women aged 65 years or older with early-stage breast cancer, enrollment in that study was discontinued early.[141] A possibility also exists that AC/CMF is not superior to no chemotherapy in this cohort. Therefore, treatment should be individualized for women in this age group, with consideration given to comorbid conditions.

Estimating Risk of Relapse or Death and Benefits of Systemic Treatment: Several prognostic factors predict for future recurrence or death from breast

cancer. The strongest prognostic factors are patient age, comorbidity, tumor size, tumor grade, number of involved axillary lymph nodes, and possibly HER2 tumor status. Algorithms have been published estimating rates of recurrence,[139] and a validated computer-based model (Adjuvant! Online at www.adjuvantonline.com) is available for estimating 10-year disease-free and overall survival that incorporates all of the above prognostic factors except HER2 tumor status.[140,142] These tools help clinicians objectively estimate both the outcome with local treatment only and the absolute benefits expected from systemic adjuvant endocrine therapy and chemotherapy. Clinicians and patients may include these estimates in their shared decision-making when considering the toxicities, costs, and benefits of systemic adjuvant therapy.[143]

Determining the HER2 status of the tumor is recommended for prognostic purposes in patients with node-negative breast cancer.[144] More importantly, HER2 tumor status also provides predictive information used when selecting optimal adjuvant/neoadjuvant therapy and therapy for recurrent or metastatic disease (category 1). For example, retrospective analyses in patients with HER2-positive tumors have shown that anthracycline-based adjuvant therapy is superior to non–anthracycline-based adjuvant chemotherapy,[145–149] and that the dose of doxorubicin may be important.[150] Prospective evidence of the predictive use of HER2 status in early-stage [151–154] and metastatic breast cancer[155–157] is available for trastuzumab-containing therapies.

DNA microarray technologies for characterizing breast cancer have allowed the development of classification systems of breast cancer according to gene expression profile.[158] Five major subtypes of breast cancer have been identified by DNA microarray gene expression profiling: ER-positive/HER2-negative (luminal A and B subtypes); ER-negative/HER2-negative (basal subtype); HER2-positive; and tumors that have characteristics similar to normal breast tissue (normal breast-like).[159–161] In retrospective analyses, these gene expression subtypes are associated with differing relapse-free and overall survival. A similar approach has been used to define more limited sets of genes for prognostic and predictive purposes.[162] For example, the MammaPrint assay uses microarray technology to analyze a 70-gene expression profile from frozen breast tumor tissue to select patients with early-stage, node-negative breast cancer who are more likely to develop distant metastases.[163–165]

Another gene-based approach is the 21-gene assay using reverse transcription polymerase chain reaction (RT-PCR) on RNA isolated from paraffin-embedded breast cancer tissue (Onco*type* DX). In a retrospective analysis of 2 trials (NSABP B-14 and B-20) involving women with hormone receptor–positive, axillary lymph node–negative invasive breast cancer, this assay system was able to quantify risk of recurrence as a continuous variable (e.g., Onco*type* DX recurrence score) and predict responsiveness to both tamoxifen and CMF or methotrexate/5-fluorouracil/leucovorin chemotherapy.[166,167] A comparison of simultaneous analyses of breast cancer tumors using 5 different gene expression models indicated that 4 of these methods (including MammaPrint and Onco*type* DX) provided similar predictions of clinical outcome.[168]

Although many DNA microarray technologies are able to stratify patients into prognostic and/or predictive subsets on retrospective analysis, the gene subsets differ among studies, and prospective clinical trials testing the efficacy of these techniques have not yet been reported. Currently, 2 prospective randomized clinical trials (TAILORx and MINDACT) are addressing the use of Onco*type* DX and MammaPrint, respectively, as predictive and/or prognostic tools in populations of women with early-stage lymph node–negative breast cancer. Pending the results of the prospective trials, the panel considers the 21-gene RT-PCR assay an option when evaluating patients with primary tumors characterized as being 0.6 to 1.0 cm with unfavorable features or larger than 1 cm, and node-negative, hormone receptor–positive, and HER2-negative (category 2A). In this circumstance, the recurrence score may be determined to help estimate likelihood of recurrence and benefit from chemotherapy (category 2B). The panel emphasizes that the recurrence score should be used in decision-making only in the context of other risk stratification elements for individual patients. All recommendations that use the recurrence score in treatment decision-making are categorized as 2B (see page 143).

Retrospective subset analysis from a single randomized clinical trial in postmenopausal axillary lymph node–positive, ER-positive breast cancer showed that the 21-gene RT-PCR assay may provide predictive information for chemotherapy benefit in

addition to tamoxifen.[169] Patient selection for assay use remains controversial (category 3).

Axillary Lymph Node–Negative Tumors: Small tumors (up to 0.5 cm in greatest diameter) that do not involve the lymph nodes are so favorable that adjuvant systemic therapy is of minimal incremental benefit and is not recommended for treating the invasive breast cancer. Endocrine therapy may be considered to reduce the risk of a second contralateral breast cancer, especially in patients with ER-positive disease. The National Surgical Adjuvant Breast and Bowel Project (NSABP) database showed a correlation between the ER status of a new contralateral breast tumor and the original primary tumor, reinforcing that endocrine therapy is unlikely to be an effective strategy for reducing the risk of contralateral breast cancer in patients diagnosed with ER-negative tumors.[170] Patients with invasive ductal or lobular tumors 0.6 to 1 cm in diameter and no lymph node involvement may be divided into patients with a low risk of recurrence and those with unfavorable prognostic features that warrant consideration of adjuvant therapy. Unfavorable prognostic features include intramammary angiolymphatic invasion, high nuclear grade, high histologic grade, HER2-positive status, or hormone receptor–negative status (category 2B). The use of endocrine therapy and chemotherapy in these relatively lower-risk subsets must be based on balancing the expected absolute risk reduction and the individual patient's willingness to experience toxicity to achieve that incremental risk reduction.

Patients with lymph node involvement or with tumors larger than 1 cm in diameter are appropriate candidates for adjuvant systemic therapy (category 1). Chemotherapy is recommended for women with lymph node–negative, hormone receptor–negative tumors larger than 1 cm in diameter (category 1). For those with lymph node–negative, hormone receptor–positive tumors larger than 1 cm, endocrine therapy with chemotherapy is recommended (category 1). Incremental benefit of combination chemotherapy in patients with lymph node–negative, hormone receptor–positive breast cancer may be relatively small.[171] Therefore, the panel recommends that tumor hormone receptor status be included as one of the factors considered when making chemotherapy-related treatment decisions for patients with node-negative, hormone receptor–positive breast cancer. Patients for whom this evaluation may be especially important are those with tumors characterized as 0.6 to 1.0 cm and hormone receptor–positive that are grade 2 or 3 or have unfavorable features, or greater than 1 cm and hormone receptor–positive and HER2-negative (see pages 142 and 143). However, chemotherapy should not be withheld from these patients solely based on ER-positive tumor status.[2,171,172]

The use of genomic/gene expression array data that also incorporate additional prognostic/predictive biomarkers (e.g., Onco*type* DX recurrence score) may provide additional prognostic and predictive information beyond anatomic staging and determination of ER/PR and HER2 status. Assessment of the role of the genomic/gene expression array technology is difficult because of the retrospective nature of the studies, the evolution of chemotherapy and hormone therapy regimens, and the overall more-favorable prognosis of patients with lymph node–negative disease compared with those enrolled in the historically controlled clinical trials. Some NCCN Member Institutions consider performing RT-PCR analysis (e.g., Onco*type* DX assay) to further refine risk stratification for adjuvant chemotherapy for patients with node-negative, ER-positive, HER2-negative breast cancers larger than 0.5 cm, whereas others do not (category 2B).

Axillary Lymph Node–Positive Tumors: Patients with lymph node–positive disease are candidates for chemotherapy and, if the tumor is hormone receptor–positive, for the addition of endocrine therapy (category 1). In postmenopausal women with hormone receptor–positive disease, an aromatase inhibitor should be used either as initial adjuvant therapy, sequential with tamoxifen, or as extended therapy after tamoxifen, unless a contraindication exists or the woman declines such therapy. In premenopausal women, adjuvant tamoxifen is recommended. If both chemotherapy and tamoxifen are administered, data from the Intergroup trial 0100 suggest that delaying initiation of tamoxifen until after completion of chemotherapy improves disease-free survival compared with concomitant administration.[172] Consequently, chemotherapy followed by endocrine therapy should be the preferred therapy sequence.

Guideline Stratification for Systemic Adjuvant Therapy: The current version of these guidelines first recognizes subsets of patients with early breast cancer of the usual histologies based on responsive-

ness to endocrine therapy and trastuzumab (i.e., hormone receptor status, HER2 status; see page 141). Patients are then further stratified based on risk for recurrence according to anatomic and pathologic characteristics (i.e., tumor grade, tumor size, axillary lymph node status, angiolymphatic invasion; see pages 142–145).

Adjuvant Endocrine Therapy: These NCCN Guidelines call for the determination of ER and PR content in all primary invasive breast cancers.[10] Patients with invasive breast cancers that are ER- or PR-positive should be considered for adjuvant endocrine therapy regardless of patient age, lymph node status, or whether adjuvant chemotherapy is to be administered.[173] Selected studies suggest that HER2-positive breast cancers may be less sensitive to some endocrine therapies, although other studies have failed to confirm this finding.[147,174–181] A retrospective analysis of tumor blocks collected in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial indicated that HER2 amplification is a marker of relative endocrine resistance independent of type of endocrine therapy.[182] However, given the favorable toxicity profile of the available endocrine therapies, the panel recommends using adjuvant endocrine therapy in most women with hormone receptor–positive breast cancer regardless of menopausal status, age, or HER2 status of the tumor. Possible exceptions to the recommendation of adjuvant endocrine therapy for patients with hormone receptor–positive disease are those patients with lymph node–negative cancers less than or equal to 0.5 cm, or 0.6 to 1.0 cm in diameter with favorable prognostic features in whom the prognosis is so favorable that the benefits of adjuvant endocrine therapy are very small.

The most firmly established adjuvant endocrine therapy is tamoxifen for both premenopausal and postmenopausal women.[2] In women with ER-positive breast cancer, adjuvant tamoxifen decreases the annual odds of recurrence by 39% and the annual odds of death by 31% irrespective of the use of chemotherapy, patient age, menopausal status, or axillary lymph node status.[2] Prospective, randomized trials show that the optimal duration of tamoxifen seems to be 5 years. In patients undergoing treatment with both tamoxifen and chemotherapy, chemotherapy should be given first, followed by sequential tamoxifen.[172]

Several studies have evaluated aromatase inhibitors in the treatment of postmenopausal women with early-stage breast cancer. These studies have used the aromatase inhibitors as initial adjuvant therapy, as sequential therapy after 2 to 3 years of tamoxifen, or as extended therapy after 4.5 to 6 years of tamoxifen. The aromatase inhibitors are not active in the treatment of women with functioning ovaries and should not be used in women whose ovarian function cannot be reliably assessed owing to treatment-induced amenorrhea (see Definition of Menopause, page 171). The results from 2 prospective, randomized clinical trials have provided evidence of an overall survival benefit for patients with early-stage breast cancer undergoing initial endocrine therapy with tamoxifen followed sequentially by anastrozole (HR, 0.53; 95% CI, 0.28–0.99; P = .045) or exemestane (HR, 0.83; 95% CI, 0.69–1.00; P = .05 [excluding patients with ER-negative disease]) when compared with tamoxifen as the only endocrine therapy.[183,184] In addition, the National Cancer Institute Canada Clinical Trials Group (NCIC CTG) MA-17 trial showed a survival advantage with extended therapy with letrozole compared with placebo in women with axillary lymph node–positive (but not lymph node–negative), ER-positive breast cancer.[185] However, no survival differences have been reported for patients undergoing initial adjuvant therapy with an aromatase inhibitor versus first-line tamoxifen.[186,187] Tamoxifen and aromatase inhibitors have different side effect profiles. Both contribute to hot flashes and night sweats, and may cause vaginal dryness. Aromatase inhibitors are more commonly associated with musculoskeletal symptoms, osteoporosis, and increased rate of bone fracture, whereas tamoxifen is associated with an increased risk of uterine cancer and deep venous thrombosis.

Two studies have examined initial adjuvant endocrine treatment with either tamoxifen or an aromatase inhibitor. The ATAC trial showed that anastrozole is superior to tamoxifen or the combination of tamoxifen and anastrozole in the adjuvant endocrine therapy of postmenopausal women with hormone receptor–positive breast cancer.[188,189] With a median of 100 months follow-up, results of 5216 postmenopausal women with hormone receptor–positive, early breast cancer enrolled in the ATAC trial showed fewer recurrences (HR for disease-free survival, 0.85; 95% CI, 0.76–0.94; P = .003) with anastrozole compared with tamoxifen.[186] No difference in survival was observed

(HR, 0.90; 95% CI, 0.75–1.07; *P* = .2). Patients in the combined tamoxifen and anastrozole group gained no benefit over those in the tamoxifen group, suggesting a possible deleterious effect from the weak estrogenic effect of tamoxifen in patients with near-complete elimination of endogenous estrogen levels.[189] ATAC trial subprotocols show a lesser effect of anastrozole compared with tamoxifen on endometrial tissue[190]; similar effects of anastrozole and tamoxifen on quality of life, with most patients reporting that their overall quality of life was not significantly impaired[191]; a greater loss of bone mineral density with anastrozole[192]; a small pharmacokinetic interference of anastrozole in the presence of tamoxifen of unclear significance[193]; and no evidence for an interaction between prior chemotherapy and anastrozole.[194]

Breast International Group (BIG) 1-98 is a randomized trial testing the use of tamoxifen alone for 5 years, letrozole alone for 5 years, or tamoxifen for 2 years followed sequentially by letrozole for 3 years, or letrozole for 2 years followed sequentially by tamoxifen for 3 years. An early analysis compared tamoxifen alone with letrozole alone, including patients in the sequential arms during their first 2 years of treatment only.[187] With 8010 women included in the analysis, disease-free survival was superior in the women treated with letrozole (HR, 0.81; 95% CI, 0.70–0.93; log rank *P* = .003). No interaction between PR expression and benefit was observed, nor was any difference in overall survival. A comparison of cardiovascular side effects in the tamoxifen and letrozole arms in the BIG 1-98 trial showed that the overall incidence of cardiac adverse events was similar (letrozole, 4.8%; tamoxifen, 4.7%). However, the incidence of grade 3 to 5 cardiac adverse events was significantly higher in the letrozole arm, and both the overall incidence and incidence of grade 3 to 5 thromboembolic events was significantly higher in the tamoxifen arm.[195] In addition, a higher incidence of bone fracture was observed for women in the letrozole arm than in the tamoxifen arm (9.5% vs. 6.5%).[196]

Four trials have studied the use of tamoxifen for 2 to 3 years followed sequentially by a third-generation aromatase inhibitor versus continued tamoxifen. The Italian Tamoxifen Anastrozole (ITA) trial randomized 426 postmenopausal women with breast cancer who had completed 2 to 3 years of tamoxifen to either continue tamoxifen or switch to anastrozole to complete a total of 5 years of endocrine therapy.[197] The hazard rate for relapse strongly favored sequential treatment with anastrozole (HR, 0.35; 95% CI, 0.18–0.68; *P* = .001) with a trend towards fewer deaths (*P* = .10).[197] Updated results from this study show the HR for relapse-free survival as 0.56 (95% CI, 0.35–0.89; *P* = .01); *P* value for overall survival analysis remained at 0.1.[198]

The Intergroup Exemestane Study (IES) trial randomized 4742 postmenopausal women with breast cancer who had completed a total of 2 to 3 years of tamoxifen to either continue tamoxifen or switch to exemestane to complete a total of 5 years of endocrine therapy.[199] The results at a median follow-up of 55.7 months showed that sequential exemestane was associated with superior disease-free survival (HR, 0.76; 95% CI, 0.66–0.88; *P* = .0001) with a significant difference in overall survival in only patients with ER-positive tumors (HR, 0.83; 95% CI, 0.69–1.00; log rank *P* = .05).

A prospectively planned, combined analysis of 3224 patients enrolled in the Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial 8 and the Arimidex Nolvadex (ARNO 95) trial also was reported.[200] After 2 years of tamoxifen, patients in this combined analysis were randomized to complete either 5 years of adjuvant tamoxifen or 3 years of anastrozole. At a median follow-up of 28 months, event-free survival was superior with crossover to anastrozole (HR, 0.60; 95% CI, 0.44–0.81; *P* = .0009). No statistically significant difference in survival was observed. An analysis of the ARNO 95 trial alone after 58 months median follow-up showed that switching from tamoxifen to anastrozole was associated with significant increases in both disease-free (HR, 0.66; 95% CI, 0.44–1.00; *P* = .049) and overall survival (HR, 0.53; 95% CI, 0.28–0.99; *P* =.045).[184] A meta-analysis of ABCSG 8, ARNO 95, and ITA studies showed significant improvement in overall survival (HR, 0.71, 95% CI, 0.52–0.98; *P* = .04) with a switch to anastrozole.[201]

Results of the MA-17 trial in 5187 women who had completed 4.5 to 6 years of adjuvant tamoxifen showed that extended therapy with letrozole provides benefit in postmenopausal women with hormone receptor–positive, early-stage breast cancer.[185,202] At a median follow-up of 2.5 years, the results showed fewer recurrences or new contralateral breast cancers with extended letrozole (HR,

0.58; 95% CI, 0.45–0.76; $P < .001$). No difference in overall survival was observed (HR, 0.82; 95% CI, 0.57–1.19; $P = .3$), although a survival advantage was seen in the subset of patients with axillary lymph node–positive disease (HR, 0.61; 95% CI, 0.38–0.98; $P = .04$). A separate cohort analysis of the MA-17 trial evaluated the efficacy of letrozole versus placebo after study unblinding in the 1579 woman who were randomly assigned to placebo after completing 4.5 to 6 years of tamoxifen.[203] The median time since completion of tamoxifen was 2.8 years. Both disease-free and distant disease-free survival were found to be significantly improved in the group receiving letrozole, thereby providing some evidence for the efficacy of letrozole in patients who have undergone 4.5 to 6 years of tamoxifen therapy followed by no endocrine therapy for an extended period. A formal quality-of-life analysis showed reasonable preservation of quality of life during extended endocrine therapy, although women may experience ongoing menopausal symptoms and loss of bone mineral density.[204,205]

The differences in design and patient populations among the studies of the aromatase inhibitors do not allow for direct comparison of the results. Thus, whether initial, sequential, or extended use of adjuvant aromatase inhibitors is the optimal strategy is unknown. The optimal duration of aromatase inhibitor treatment is also not known, nor is the optimal use vis-à-vis chemotherapy established. Furthermore, the long-term (> 5 years) safety and efficacy of these agents are still under investigation. The various studies consistently show that the use of a third-generation aromatase inhibitor in postmenopausal women with hormone receptor–positive breast cancer lowers the risk for recurrence, including ipsilateral breast tumor recurrence, contralateral breast cancer, and distant metastatic disease, compared with tamoxifen alone when the aromatase inhibitor is used as initial adjuvant, sequential, or extended therapy. Thus, the current guidelines recommend that postmenopausal women with early-stage breast cancer receive an aromatase inhibitor as initial adjuvant therapy, sequential with tamoxifen, or as extended therapy when endocrine therapy is to be used. The panel found no compelling evidence that meaningful efficacy or toxicity differences exist among anastrozole, letrozole, and exemestane. In postmenopausal women, the use of tamoxifen alone for 5 years is limited to those who decline or have a contraindication to aromatase inhibitors (see page 165).

It should be reemphasized that the aromatase inhibitors are associated with the development of benign ovarian pathology and do not adequately suppress ovarian estrogen synthesis in women with functioning ovaries. Premenopausal women should not be given therapy with an aromatase inhibitor outside the confines of a clinical trial. Women who are premenopausal at diagnosis and who become amenorrheic with chemotherapy may have continued estrogen production from the ovaries in the absence of menses. Serial assessment of circulating luteinizing hormone, follicle-stimulating hormone, and estradiol to assure a true postmenopausal status is mandatory if this subset of women is to be considered for therapy with an aromatase inhibitor[206,207] (see page 171).

Adjuvant Cytotoxic Chemotherapy: Several combination chemotherapy regimens are appropriate to consider when adjuvant cytotoxic chemotherapy is used (see pages 166–170). All adjuvant chemotherapy regimens listed in the NCCN Guidelines have been evaluated in phase III clinical trials, and the current version of the adjuvant chemotherapy guideline does not distinguish between options for chemotherapy regimens according to axillary lymph node status. The regimens listed as *preferred* include docetaxel, doxorubicin, and cyclophosphamide (TAC); AC; dose-dense AC with sequential paclitaxel; AC followed by weekly paclitaxel; and docetaxel plus cyclophosphamide (TC). Other regimens included in the guidelines are fluorouracil, doxorubicin, and cyclophosphamide (FAC/CAF) or cyclophosphamide, epirubicin, and fluorouracil (FEC/CEF); epirubicin and cyclophosphamide (EC); CMF; AC with sequential docetaxel administered every 3 weeks; doxorubicin, paclitaxel, and cyclophosphamide each as a single agent for 4 cycles given every 2 weeks (dose-dense A – T – C); FEC followed by docetaxel; and FEC followed by weekly paclitaxel. The adjuvant chemotherapy guideline also includes specific representative doses and schedules for the recommended adjuvant chemotherapy regimens (see pages 166–170). Recent studies document substantial improvement in outcome with the incorporation of trastuzumab in the adjuvant treatment of HER2-positive breast cancer (see Adjuvant Trastuzumab Therapy, facing page).

The purpose of distinguishing between *preferred*

and *other* adjuvant chemotherapy regimens is to convey the panel's opinion regarding the relative efficacy and toxicity of the regimens.[208] Factors considered by the panel include the efficacy, toxicity, and treatment schedules of the regimens. This initial attempt at categorizing preferred regimens will be followed in the future by a more comprehensive, systematic evaluation of comparative effectiveness, which will also include cost considerations. Results of clinical trials focusing on treatment efficacy are summarized below.

Studies of CMF chemotherapy versus no chemotherapy have shown disease-free and overall survival advantages with CMF chemotherapy.[2,209] Studies using CAF/FAC chemotherapy have shown that the use of full-dose chemotherapy regimens is important.[210] In the Early Breast Cancer Trialists' overview of polychemotherapy, comparison of anthracycline-containing regimens with CMF showed a 12% further reduction in the annual odds of recurrence (P = .006) and an 11% further reduction in the annual odds of death (P = .02) with anthracycline-containing regimens.[209] Based on these data, the panel qualified the appropriate chemotherapy regimens by the statement that anthracycline-containing regimens are preferred for patients with node-positive tumors. The Early Breast Cancer Trialists' analysis, however, did not consider the potential interaction between HER2 tumor status and efficacy of anthracycline-containing versus CMF chemotherapy regimens. Retrospective analysis has suggested that the superiority of anthracycline-containing chemotherapy may be limited to the treatment of breast cancers that are HER2-positive.[144,146,149,179,211–213] The retrospective finding across several clinical trials that anthracycline-based chemotherapy may be more efficacious in patients whose tumors are HER2-positive has led to a footnote stating that anthracycline-based chemotherapy may be superior to non–anthracycline-containing regimens in the adjuvant treatment of these patients (see pages 166–170).

AC chemotherapy for 4 cycles has been studied in randomized trials, resulting in relapse-free and overall survival equivalent to CMF chemotherapy.[214–216] No benefit from dose escalation of either doxorubicin or cyclophosphamide was shown.[217,218]

The results of 2 randomized trials comparing AC chemotherapy with or without sequential paclitaxel chemotherapy in women with axillary node–positive breast cancer suggest improved disease-free rates, and results from one showed an improvement in overall survival, with the addition of paclitaxel.[218,219] On retrospective analysis, the apparent advantage of the paclitaxel-containing regimen seems greater in women with ER-negative breast cancers.

A randomized trial evaluated the use of concurrent versus sequential chemotherapy (doxorubicin followed by paclitaxel followed by cyclophosphamide versus doxorubicin plus cyclophosphamide followed by paclitaxel) given either every 2 weeks with filgrastim support versus every 3 weeks. The results show no significant difference between the 2 chemotherapy regimens, but show a 26% reduction in hazard of recurrence (P = .01) and a 31% reduction in the hazard of death (P = .013) for the dose-dense regimens.[220]

Two randomized prospective trials of CEF chemotherapy in axillary lymph node–positive breast cancer are available. In one trial, premenopausal women with node-positive breast cancer were randomized to undergo classic CMF therapy versus CEF chemotherapy using high-dose epirubicin. Both 10-year relapse-free (52% vs. 45%; P = .007) and overall survival (62% vs. 58%; P = .085) favored the CEF arm.[221] The second trial compared CEF given all intravenously every 3 weeks at 2 dose levels of epirubicin (50 vs. 100 mg/m^2) in premenopausal and postmenopausal women with node-positive breast cancer. Five-year disease-free (55% vs. 66%; P = .03) and overall survival (65% vs. 76%; P = .007) both favored the epirubicin 100 mg/m^2 arm.[222] Another trial compared 2 dose levels of EC chemotherapy with CMF chemotherapy in women with node-positive breast cancer.[223] This study showed that higher-dose EC chemotherapy was equivalent to CMF chemotherapy and superior to moderate-dose EC in event-free and overall survival. Another randomized trial in women with axillary lymph node–positive breast cancer compared 6 cycles of FEC with 3 cycles of FEC followed by 3 cycles of docetaxel.[224] Five-year disease-free (78.4% vs. 73.2%; adjusted P = .012) and overall survivals (90.7% vs. 86.7%; P = .017) were superior with sequential FEC followed by docetaxel. However, no significant disease-free survival differences were seen in a recent large randomized study comparing adjuvant chemotherapy with 4 cycles of every-3-weekly FEC followed by 4 cycles of every-3-weekly docetaxel with standard anthracycline chemotherapy regimens (e.g., FEC or epirubicin followed by CMF) in women

with node-positive or high-risk node-negative operable breast cancer.[225]

Final results from a randomized trial comparing TAC and FAC chemotherapy in axillary lymph node–positive breast cancer showed that TAC was superior to FAC.[226] Estimated 5-year disease-free survival rates were 75% with TAC and 68% with FAC (HR, 0.72; 95% CI, 0.59–0.88; P = .001), and overall survival rates were 87% and 81% with FAC, respectively (HR, 0.70; 95% CI, 0.53–0.91; P = .008). Disease-free survival favored TAC in both ER-positive and -negative tumors.

At a median follow-up of 73 months, results from the 3-arm randomized NSABP B-30 trial comparing TAC versus doxorubicin in combination with either docetaxel or paclitaxel (AT) versus AC followed by docetaxel (AC→T) showed that AC→T had significant advantage in disease-free (HR, 0.83; P = .006) but not overall survival (HR, 0.86; P = .086) when compared with TAC. In addition, both disease-free (HR, 0.080; P = .001) and overall survival (HR, 0.83; P = .034) were significantly increased when AC→T was compared with AT, with AT showing noninferiority compared with TAC.[227]

The ECOG E1199 study was a 4-arm trial that randomized 4950 women to receive AC chemotherapy followed by either paclitaxel or docetaxel using either an every-3-weekly or a weekly schedule.[228,229] At a median 63.8 months follow-up, no statistically significant differences in disease-free or overall survival were observed when comparing paclitaxel with docetaxel, or weekly versus every-3-weekly administration. In a secondary series of comparisons, weekly administration of paclitaxel was superior to every-3-weekly in disease-free (HR, 1.27; 95% CI, 1.03–1.57; P = .006) and overall survival (HR, 1.32; 95% CI, 1.02–1.72; P = .01), and every-3-weekly docetaxel was superior to every-3-weekly paclitaxel in disease-free survival (HR, 1.23; 95% CI, 1.00–1.52; P = .02) but not in overall survival.[229] Based on these results and the findings from CALGB 9741, which showed dose-dense AC followed by paclitaxel every 2 weeks had a survival benefit compared with AC followed by paclitaxel every 3 weeks,[220] the every-3-weekly paclitaxel regimen was removed from these guidelines.

One trial randomizing 1016 women with stage I to III breast cancer to either TC or AC chemotherapy[230] showed that overall disease-free (81% vs. 75%; P = .033; HR, 0.74; 95% CI, 0.56–0.98) and overall survival rates (87% vs. 82%; P = 0.032; HR, 0.69; 95% CI, 0.50–0.97) at a median follow-up of 7 years were significantly improved with TC.

The addition of weekly paclitaxel after FEC was shown to be superior to FEC alone in a randomized study of 1246 women with early-stage breast cancer.[231] The former regimen was associated with a 23% reduction in the risk of relapse compared with FEC (HR, 0.77; 95% CI, 0.62–0.95; P = .022), although no significant difference in overall survival was seen when the 2 arms were compared at a median follow-up of 66 months.

Several retrospective studies have evaluated the potential interaction of chemotherapy benefit and ER status.[2,171] These studies assessed the effect of chemotherapy on the risk of breast cancer recurrence in patients with ER-positive tumors undergoing adjuvant endocrine therapy compared with those with ER-negative tumor status not undergoing adjuvant endocrine therapy. These analyses suggest that the benefits of chemotherapy are significantly greater in patients with ER-negative disease. For example, Berry et al.[171] showed that 22.8% more patients with ER-negative tumors survived without disease for 5 years if they received chemotherapy; this benefit was only 7% for patients with ER-positive tumors receiving chemotherapy. These guidelines therefore include a recommendation for endocrine therapy and consideration of chemotherapy for patients with node-negative disease and tumors characterized as ER-positive that are larger than 1 cm and HER2-negative, or tumors 0.6 to 1.0 cm that are grade 2 or 3 or have unfavorable features (see page 143).

Adjuvant Trastuzumab Therapy: Trastuzumab is a humanized, monoclonal antibody with specificity for the extracellular domain of HER2/neu, or HER2.[232] Results of 5 randomized trials testing trastuzumab as adjuvant therapy have been reported.[151–154] In NSABP B-31, patients with HER2-positive, node-positive breast cancer were randomly assigned to 4 cycles of AC every 3 weeks followed by 4 cycles of paclitaxel every 3 weeks, or the same regimen with 52 weeks of trastuzumab commencing with the paclitaxel. In the North Central Cancer Treatment Group (NCCTG) N9831 trial, patients with HER2-positive breast cancer that was node-positive or, if node-negative with primary tumors larger than 1 cm if ER- and PR-negative or greater than 2 cm in

size if ER- or PR-positive, were similarly randomized, except that paclitaxel was given using a low-dose weekly schedule for 12 weeks, and a third arm delayed trastuzumab until completion of paclitaxel. The NSABP B-31 and NCCTG N9831 trials were jointly analyzed, and the merged control arms for both trials compared with the merged arms using trastuzumab begun concurrently with paclitaxel. This joint analysis included 3968 patients and was performed at median follow-up of 4 years. A 52% reduction in recurrence risk (HR, 0.48; 95% CI, 0.41–0.57; $P < .0001$) and 35% reduction in the risk of death (HR, 0.65; 95% CI, 0.51–0.84; log rank $P = .0007$) were documented.[233] Similar significant effects on disease-free survival were observed when results of the NSABP B-31 and NCCTG N9831 trials were analyzed separately. Cardiac toxicity was increased in patients treated with trastuzumab.[153,234,235]

In the adjuvant trastuzumab trials, the rates of grade III/IV congestive heart failure or cardiac-related death for patients undergoing treatment regimens containing trastuzumab ranged from 0% (FinHer trial) to 4.1% (NSABP B-31 trial) overall.[151–154,234,235] The frequency of cardiac dysfunction seems to be related to both age and baseline left ventricular ejection fraction. An analysis of data from N9831 showed the 3-year cumulative incidence of congestive heart failure or cardiac death to be 0.3%, 2.8%, and 3.3% in the trial arms without trastuzumab, with trastuzumab after chemotherapy, and with trastuzumab initially combined with paclitaxel, respectively.[234] The acceptable rate of significant cardiac toxicity observed in the trastuzumab adjuvant trials partly reflects rigorous monitoring for cardiac dysfunction. Furthermore, concerns have been raised regarding the long-term cardiac risks associated with trastuzumab therapy based on results of follow-up evaluations of cardiac function in patients enrolled in some of these trials.[236,237]

A third trial (Herceptin Adjuvant trial [HERA]; N = 5081) tested trastuzumab for 1 or 2 years compared with none after all local therapy and various standard chemotherapy regimens in patients with node-positive disease, or node-negative disease with tumors 1 cm or larger.[152] At 1-year median follow-up, 1 year of trastuzumab resulted in a 46% reduction in recurrence risk (HR, 0.54; 95% CI, 0.43–0.67; $P < .0001$), no difference in overall survival, and acceptable cardiac toxicity when compared with no trastuzumab. The 2-year data indicate that 1 year of trastuzumab therapy is associated with an overall survival benefit compared with observation (HR for risk of death, 0.66; 95% CI, 0.47–0.91; $P = .0115$).[238]

The Breast Cancer International Research Group (BCIRG) 006 study randomized 3222 women with HER2-positive, node-positive, or high-risk node-negative breast cancer to AC followed by docetaxel, AC followed by docetaxel plus trastuzumab for 1 year, or carboplatin and docetaxel plus trastuzumab for 1 year.[154] At 36 months of follow-up, patients receiving AC followed by docetaxel with trastuzumab (AC→TH) had an HR for disease-free recurrence of 0.61 (95% CI, 0.48–0.76; $P < .0001$) compared with the the control arm receiving the same chemotherapy regimen without trastuzumab (AC→T). The HR for disease-free survival was 0.67 (95% CI, 0.54–0.83; $P = .0003$) when patients in the carboplatin/docetaxel/trastuzumab (TCH)-containing arm were compared with those in the control arm. No statistically significant difference in the HR for disease-free survival was observed between the 2 trastuzumab-containing arms. An overall survival advantage was reported for patients in both trastuzumab-containing arms relative to the control arm (HR for AC→TH vs. AC→T = 0.59; 95% CI, 0.42–0.85; $P = .004$; HR for TCH vs. AC→T = 0.66; 95% CI, 0.47–0.93; $P = .017$). Cardiac toxicity was significantly lower in the TCH arm (8.6% patients with > 10% relative decline in left ventricular ejection fraction) compared with the AC→TH arm (18%; $P < .0001$); differences in cardiac toxicity between the TCH arm and the AC→T control arm (10%) were not significant.

A fifth trial (Finland Herceptin [FinHer]) randomized 1010 women to either 9 weeks of vinorelbine followed by 3 cycles of FEC chemotherapy versus docetaxel for 3 cycles followed by 3 cycles of FEC chemotherapy.[151] Patients with HER2-positive cancers that were either node-positive or node-negative and 2 cm or larger and PR-negative (n = 232) were further randomized to treatment or no treatment with trastuzumab for 9 weeks during the vinorelbine or docetaxel portions of the chemotherapy only. With a median follow-up of 3 years, the addition of trastuzumab was associated with a reduction in risk of recurrence (HR, 0.42; 95% CI, 0.21–0.83; $P = .01$). No statistically significant differences in overall survival (HR, 0.41; 95% CI, 0.16–1.08; $P = .07$) or cardiac toxicity were observed with the addition of trastuzumab.[151] At 5 years

follow-up, a comparison of the 2 arms (i.e., chemotherapy with and without trastuzumab) showed that the HRs for distant disease-free survival (HR, 0.65; 95% CI, 0.38–1.12; $P = .12$) and overall survival (HR, 0.55; 95% CI, 0.27–1.11; $P = .094$) were higher relative to those reported at 3 years.[239]

All of the adjuvant trials of trastuzumab show clinically significant improvements in disease-free survival, and the combined analysis from the NSABP B31 and NCCTG N9831 trials, and the HERA trial, showed significant improvement in overall survival with the use of trastuzumab in patients with high-risk, HER2-positive breast cancer. Therefore, regimens from each of these trials are included as trastuzumab-containing adjuvant regimen choices in the NCCN Guidelines (category 1; see pages 166–170). The benefits of trastuzumab are independent of ER status.[153] Based on these studies, the panel has designated use of trastuzumab with chemotherapy as a category 1 recommendation in patients with HER2-positive tumors larger than 1 cm.

The panel recommends AC followed by paclitaxel with trastuzumab for 1 year commencing with the first dose of paclitaxel as a preferred trastuzumab-containing adjuvant regimen, because this regimen showed efficacy in 2 randomized clinical trials and was associated with significant improvements in overall survival. The TCH regimen is also classified as a preferred regimen, especially in patients with risk factors for cardiac toxicity, given the results of BCIRG 006 study that showed superior disease-free survival in patients receiving either TCH or AC followed by docetaxel plus trastuzumab both, compared with AC followed by docetaxel alone. Because patients with borderline FISH (PathVysion) scores of greater than 2.0 to 2.2 *HER2* genes/chromosome 17/cell in early-stage breast cancer were eligible for the adjuvant trials, the panel cannot recommend excluding these patients from adjuvant treatment with trastuzumab if HER2 tumor status remains equivocal after retesting using the same or a complementary method (see page 159).

The panel also recommended that adjuvant trastuzumab be considered in women with node-negative tumors that are 0.6 to 1.0 cm (category 2A; see pages 142 and 144). Some support for this recommendation comes from results of a retrospective study of 1245 women with early-stage breast cancer tumors characterized as T1pN0.[240] In women with HER2-positive, ER-positive tumors, 10-year breast cancer–specific survival rates and 10-year recurrence-free survival rates were 85% and 75%, respectively, compared with 70% and 61%, respectively, in women with HER2-positive, ER-negative tumors. Two more recent retrospective studies have also investigated recurrence-free survival in this patient population. In one large study, 5-year recurrence-free survival rates of 77.1% and 93.7% ($P < .001$) were observed for patients with HER2-positive and HER2-negative T1a,bN0M0 breast tumors, respectively, with no recurrence-free survival differences seen in the HER2-positive group when hormonal receptor status was considered.[241] In another retrospective study of women with small HER2-positive tumors, the risk of recurrence at 5 years was low, although disease-free survival was inferior in the group with HER2-positive, hormone receptor–positive disease.[242] None of the patients in these 2 retrospective studies had received trastuzumab. Subgroup analyses from several of the randomized trials have shown consistent benefit of trastuzumab irrespective of tumor size or nodal status.[233,243] The recommendation for consideration of trastuzumab in patients with HER2-positive tumors that are 0.6 to 1.0 cm is now designated as category 2A.

Dose-dense AC→T with trastuzumab is another trastuzumab-containing adjuvant chemotherapy regimen included in these guidelines. Data from a single-arm study of 70 patients support the safety and feasibility of this regimen.[244]

Finally, no statistically significant disease-free or overall survival benefit for the addition of trastuzumab was observed in the FNCLCC-PACS-04 trial, in which 528 women with HER2-positive, node-positive breast cancer were randomly assigned to either receive trastuzumab or undergo observation after completion of adjuvant anthracycline-based chemotherapy with or without docetaxel.[245] These results suggest that the sequential administration of trastuzumab after chemotherapy is not as efficacious as a schedule involving concomitant chemotherapy and trastuzumab.

Adjuvant Therapy of Favorable Histology Tumors: These NCCN Guidelines provide systemic treatment recommendations for the favorable-histology invasive breast cancers, such as tubular and colloid cancers, based on tumor size and axillary lymph node status (see page 146). If used, the treatment options

for endocrine therapy, chemotherapy, and sequencing of treatment with other modalities are similar to those of the usual histology breast cancers. Most tubular breast cancers are both ER-positive and HER2-negative. Thus, the pathology evaluation and accuracy of the ER and/or HER2 determination should be reviewed if a tubular breast cancer is found to be ER-negative and/or HER2-positive, or if a tumor with an ER- and PR-negative status is found to be grade 1.[10] If a breast cancer is histologically identified as a tubular or colloid (mucinous) breast cancer and confirmed as ER-negative, then the tumor should be treated according to the guideline for the usual-histology, ER-negative breast cancers. The panel acknowledges that prospective data on systemic adjuvant therapy of favorable histology tumors are lacking.

Medullary carcinoma is an uncommon variant of infiltrating ductal carcinoma characterized by high nuclear grade, lymphocytic infiltration, a pushing tumor border, and the presence of a syncytial growth pattern. Experts previously believed that medullary carcinoma has a lower potential for metastases and a better prognosis than typical infiltrating ductal carcinoma. However, the best available evidence suggests that the risk of metastases equals that of other high-grade carcinomas, even cases that meet all the pathologic criteria for typical medullary carcinoma. Furthermore, typical medullary carcinoma is uncommon, and marked interobserver variation occurs in diagnosing this entity.

Many cases classified as medullary carcinoma do not have all the pathologic features on subsequent pathologic review. Given these facts, concern exists that patients may be harmed if a high-grade infiltrating ductal carcinoma is misclassified as typical medullary carcinoma and this classification used as the basis for withholding otherwise indicated adjuvant systemic therapy. Therefore, the panel believes that including medullary carcinoma with other special-histology cancers that confer a very favorable prognosis and often do not require systemic therapy is not appropriate. The panel recommends that cases classified as medullary carcinoma be treated as other infiltrating ductal carcinomas based on tumor size, grade, and lymph node status.

Stage III Invasive Breast Cancer

The staging evaluation for most patients with stage III invasive breast cancer is similar to that for patients with T3N1M0 disease (see pages 138 and 151). The workup includes history and physical exam, a complete blood cell count, platelet count, liver function and alkaline phosphatase tests, chest imaging, pathology review, prechemotherapy determination of tumor ER/PR receptor status and HER2 status, diagnostic bilateral mammogram, and breast ultrasound as clinically warranted. Genetic counseling is recommended if the patient is considered to be at high risk of 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 the NCCN Web site at www.NCCN.org).

The performance of other studies, such as a breast MRI, a bone scan (category 2B), and abdominal imaging with CT (with or without pelvic CT), ultrasound, or MRI (all category 2A) are optional unless directed by symptoms or other abnormal study results. PET/CT scan is also included as an optional additional study (category 2B).

Panel consensus is that PET/CT is most helpful when standard imaging results are equivocal or suspicious. However, limited recent studies[40,41,246–249] support a potential role for FDG PET/CT to detect regional node involvement and distant metastases in locally advanced breast cancer, including T3N1M0 disease.

Equivocal or suspicious sites identified with PET/CT scanning should be biopsied for confirmation whenever possible, and the site of disease will impact the course of treatment. In the past decade, the advent of PET/CT scanners has significantly changed the approach to PET imaging.[250] However, the terminology has also created confusion regarding the nature of the scans obtained from a PET/CT device. PET/CT scanners have both a PET and CT scanner in the same gantry that allows precise coregistration of molecular (PET) and anatomic (CT) imaging. Almost all current clinical PET imaging is performed using combined PET/CT devices.

In PET/CT tomographs, the CT scanner has a second important role beyond diagnostic CT scanning.[250] For PET applications, the CT scan is also used for photon attenuation correction and for anatomic localization of the PET imaging findings. For these tasks, the CT scan is usually taken without breathholding, to match PET image acquisition, and typically uses relatively low-dose (nondiagnostic) CT. Radiation exposure for these nondiagnostic CT scans is lower than for diagnostic CT. Intravenous

contrast is not needed for this task.

PET/CT scanners typically include a high-quality CT device that can also be used for standalone, optimized, and fully diagnostic CT. Diagnostic CT scans are acquired using breathholding for optimal chest imaging, and are often performed with intravenous contrast. For fully diagnostic CT, the CT beam current, and therefore patient radiation exposure, is considerably higher than for the low-dose CT needed for PET requirements. Radiation exposures for fully diagnostic CT are often greater than for the emission (PET) component of the study.

Currently, the approach to clinical PET/CT imaging varies widely across centers.[251] Many centers perform low-dose CT as part of a PET/CT scan, and perform optimized, fully diagnostic CT only when diagnostic CT has also been requested in addition to PET/CT. Other centers combine diagnostic CT scans with PET on all of their PET/CT images. The CT scans described on pages 138, 147, and 151 refer to fully optimized diagnostic CT scans, whereas the PET or PET/CT scans refer to scans primarily directed toward the PET component, not necessarily using diagnostic-quality CT. It is important for referring physicians to understand the differences between PET/CT performed primarily for PET imaging and fully optimized CT performed as a standalone diagnostic CT examination.[251]

Operable Locally Advanced Breast Cancer (Clinical Stage T3N1M0): Locally advanced breast cancer describes a subset of invasive breast cancer in which the initial clinical and radiographic evaluation documents advanced disease confined to the breast and regional lymph nodes. The AJCC clinical staging system used in these NCCN Guidelines and for the determination of operability is recommended, and locally advanced disease is represented by the stage III category. Patients with stage III disease may be further divided into those for whom an initial surgical approach is unlikely to remove all disease or provide long-term local control and those for whom a reasonable initial surgical approach is likely to achieve pathologically negative margins and provide long-term local control. Thus, patients with stage IIIA disease are divided into those who have clinical T3N1M0 disease and those who have clinical TanyN2M0 disease, based on multidisciplinary evaluation. For patients with operable locally advanced disease, which are generally those with clinical T3N1M0 disease, treatment is as outlined on pages 138 through 143.

Postsurgical systemic adjuvant therapy for patients with stage IIIA breast cancer who do not undergo neoadjuvant chemotherapy is similar to that for patients with stage II disease.

Inoperable Locally Advanced Breast Cancer (Clinical Stage IIIA [Except for T3N1M0], IIIB, or IIIC): The workup of locally advanced breast cancer is described on page 151. For patients with inoperable noninflammatory locally advanced disease at presentation, the initial use of anthracycline-based preoperative chemotherapy with or without a taxane is standard therapy.[252] Patients with locally advanced breast cancer that is HER2-positive should be treated with an initial chemotherapy program that incorporates preoperative trastuzumab (pages 166–170). Local therapy after a clinical response to preoperative chemotherapy usually consists of either total mastectomy with level I/II axillary lymph node dissection, with or without delayed breast reconstruction, or lumpectomy and level I/II axillary dissection. Both local treatment groups are considered to have sufficient risk of local recurrence to warrant the use of chest wall (or breast) and supraclavicular node irradiation. If internal mammary lymph nodes are involved, they should also be irradiated. In the absence of detected internal mammary node involvement, including the internal mammary lymph nodes in the radiation field may be considered (category 3; see page 152).

Adjuvant therapy may involve completion of a planned chemotherapy regimen course if not completed preoperatively, followed by endocrine therapy in patients with hormone receptor–positive disease (see page 152). Up to 1 year of total trastuzumab therapy should be completed if the tumor is HER2-positive (category 1). Endocrine therapy and trastuzumab can be administered concurrently with radiation therapy if indicated.

Patients with an inoperable stage III tumor with disease progression during preoperative chemotherapy should be considered for palliative breast irradiation in an attempt to enhance local control. In all subsets of patients, further systemic adjuvant chemotherapy after local therapy is believed to be standard. Tamoxifen (or an aromatase inhibitor if postmenopausal) should be added for those with hormone receptor–positive tumors, and trastuzumab should

be given to those with HER2-positive tumors. Posttreatment follow-up for women with stage III disease is the same as for those with earlier-stage invasive breast cancer. Treatment recommendations for inflammatory locally advanced breast cancer are described in the section on inflammatory breast cancer, which can be found in the full NCCN Guidelines for Breast Cancer, available online at www.NCCN.org (page IBC-1).

Posttherapy Surveillance and Follow-up

Posttherapy follow-up is optimally performed by members of the treatment team and includes regular physical examinations and mammography. In patients undergoing breast-conserving therapy, mammography should be performed annually (category 2A). Routine alkaline phosphatase and liver function tests are not included in these guidelines.[253–255] In addition, the panel notes no evidence supporting the use of tumor markers for breast cancer, and that routine bone, CT, MRI, or PET scans or ultrasound examinations in asymptomatic patients provide no advantage in survival or ability to palliate recurrent disease and therefore are not recommended.[40,256]

The use of dedicated breast MRI may be considered an option for posttherapy surveillance and follow-up in women at high risk of bilateral disease, such as carriers of *BRCA1/2* mutations. Rates of contralateral breast cancer after either breast-conserving therapy or mastectomy have been reported to be increased in women with *BRCA1/2* mutations when compared with patients with sporadic breast cancer[257–259](see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian and NCCN Guidelines for Breast Cancer Screening and Diagnosis; to view the most recent version of these guidelines, visit www.NCCN.org).

The panel recommends that women with intact uteri who are taking tamoxifen should have yearly gynecologic assessments and rapid evaluation of any vaginal spotting that might occur because of the risk of tamoxifen-associated endometrial carcinoma in postmenopausal women[260](see page 153). Routine endometrial biopsy or ultrasonography in asymptomatic women is not recommended. Neither test has shown efficacy as a screening test in any population of women. Most women with tamoxifen-associated uterine carcinoma experience early vaginal spotting.

Symptom management for women undergoing adjuvant endocrine therapies often requires treatment of hot flashes and concurrent depression. Venlafaxine has specifically been studied and is an effective intervention in decreasing hot flashes.[261] Recent evidence suggests that concomitant use of tamoxifen with certain selective serotonin reuptake inhibitors (SSRIs; e.g., paroxetine, fluoxetine) may decrease plasma levels of endoxifen, an active metabolite of tamoxifen.[262,263] These SSRIs may interfere with the enzymatic conversion of tamoxifen to endoxifen by inhibiting a particular isoform of cytochrome P-450 enzyme (CYP2D6) involved in the metabolism of tamoxifen. However, the SSRIs citalopram, escitalopram, fluvoxamine, gabapentin, sertraline, and venlafaxine seem to have no or only minimal effect on tamoxifen metabolism.[206,264] If an aromatase inhibitor is considered in women with amenorrhea after treatment, baseline levels of estradiol and gonadotropin followed by serial monitoring of these hormones should be performed if endocrine therapy with an aromatase inhibitor is initiated[206] (see page 171). Bilateral oophorectomy assures postmenopausal status in young women with therapy-induced amenorrhea and may be considered before initiating therapy with an aromatase inhibitor.

Follow-up also includes assessment of patient adherence to ongoing medication regimens, such as endocrine therapies. Predictors of poor adherence to medication include the presence of side effects associated with the medication, and incomplete understanding by the patient of the benefits associated with regular administration of the medication.[265] The panel recommends implementation of simple strategies to enhance patient adherence to endocrine therapy, such as direct questioning of the patient during office visits; brief, clear explanations of the value of taking the medication regularly; and the therapeutic importance of longer durations of endocrine therapy (see page 153).

Evidence suggests that a healthy lifestyle may lead to better breast cancer outcomes. A nested case control study of 369 women with ER-positive tumors who developed a second primary breast cancer compared with 734 matched control patients who did not develop a second primary tumor, showed an association among obesity (BMI ≥ 30), smoking, and alcohol consumption and contralateral breast cancer.[266] A prospective study of 1490 women diagnosed with stage I through III breast cancer showed an association among high fruit and vegetable consumption,

physical activity, and improved survivorship, regardless of obesity.[267] Thus, the panel recommends an active lifestyle and ideal body weight (BMI, 20–25) for optimal overall health and breast cancer outcomes.

Many young women treated for breast cancer remain or regain premenopausal status after treatment for breast cancer. For these women, the panel discourages the use of hormonal birth control methods, regardless of the hormone receptor status of the tumor.[268] Alternative birth control methods are recommended, including intrauterine devices, barrier methods, and, for those with no plans for future pregnancy, tubal ligation or vasectomy for the partner. Breastfeeding during endocrine or chemotherapy treatment is not recommended by the panel because of risks to the infant. Breastfeeding after breast-conserving treatment for breast cancer is not contraindicated. However, lactation from an irradiated breast may not be possible, or may occur only with a diminished capacity[268,269] (see page 160).

Stage IV Metastatic or Recurrent Breast Cancer

The staging evaluation of women who present with metastatic or recurrent breast cancer includes a history and physical examination, complete blood cell count, platelet count, liver function tests, chest imaging, bone scan, radiographs of any long or weight-bearing bones that are painful or appear abnormal on bone scan, consideration of CT or MRI scan of the abdomen, biopsy documentation of first recurrence if possible, and determination of hormone receptor status (ER and PR). HER2 status should be repeated, especially if unknown, originally negative, or not overexpressed. Genetic counseling is recommended for patients considered to be at high risk of 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 the NCCN Web site at www.NCCN.org).

The panel generally discourages using PET or PET/CT scans to evaluate patients with recurrent disease, except when other staging studies are equivocal or suspicious. Although only limited and mostly retrospective evidence supports the use of PET/CT scanning to guide treatment planning through determining the extent of disease in select patients with recurrent or metastatic disease,[40,41,270,271] the panel considers biopsy of equivocal or suspicious sites to be more likely than PET/CT scanning to provide accurate staging information in these patients.

Local Disease Only

Patients with local recurrence only are divided into those who 1) were treated initially with mastectomy alone, 2) had mastectomy and radiation therapy, and 3) underwent breast-conserving therapy (see page 153).

In one retrospective study of local recurrence patterns in women with breast cancer who had undergone mastectomy and adjuvant chemotherapy without radiation therapy, the most common sites of local recurrence were the chest wall and the supraclavicular lymph nodes.[272] The recommendations for treatment of patients experiencing only local recurrence are supported by analyses of a combined database of patients from the EORTC 10801 and Danish Breast Cancer Group 82TM trials. The analyses compared breast-conserving therapy with mastectomy in patients with stage I and II disease. The 133 (~ 8%) patients experiencing a local recurrence as an initial event were approximately equally divided between those who had undergone mastectomy and those who had undergone breast-conserving therapy as initial treatment for breast cancer. Of those in the former group, 51 (76%) were able to undergo radiation therapy with or without surgery as treatment for local disease recurrence. No difference in survival emerged when patients undergoing salvage treatment after initial treatment with mastectomy or breast-conserving therapy were compared; approximately 50% of both groups were alive at 10 years.[273]

Patients treated with mastectomy should undergo surgical resection of the local recurrence (if it can be accomplished without heroic surgery) and involved-field radiation therapy to the chest wall and supraclavicular area (if the chest wall was not previously treated or if additional radiation therapy may be safely administered). Surgical resection in this setting implies the use of limited excision of disease with the goal of obtaining clear margins of resection. Unresectable chest wall recurrent disease should be treated with radiation therapy if none was given prior to radiation. Women experiencing a local recurrence after initial breast-conserving therapy should undergo a total mastectomy and axillary staging if a level I/II axillary dissection was not previously performed. Limited data suggest that a repeat sentinel lymph node biopsy after local recurrence of disease may be successfully performed in 80% of women who have

previously undergone breast-conserving therapy and sentinel node biopsy.[274] The panel agrees that the preferred surgical approach for most women with a local recurrence after breast-conserving therapy and sentinel node biopsy is mastectomy and a level I/II axillary dissection, although sentinel node biopsy in lieu of a level I/II axillary dissection can be considered if prior axillary staging was performed through sentinel node biopsy only.

After local treatment, women with only local recurrences should be considered for limited duration systemic chemotherapy or endocrine therapy similar to that outlined in the adjuvant chemotherapy section. The ongoing BIG 1-01/IBCSG 27-02/NSABP B-37 study is evaluating the efficacy of chemotherapy in women who develop an isolated local and/or regional ipsilateral recurrence after primary treatment for early-stage breast cancer.[275] The panel emphasizes the importance of individualizing treatment strategies for patients with a recurrence limited to a local site.

These guidelines recommend the consideration of adding hyperthermia to irradiation for localized recurrences/metastasis (category 3; see page 154). Several prospective randomized trials have compared radiation alone with radiation plus hyperthermia in the treatment of locally advanced/recurrent cancers, primarily breast cancer chest wall recurrences.[276,277] Although heterogeneity exists among the study results, a recent series with strict quality assurance showed a statistically significant increase in local tumor response and greater duration of local control with the addition of hyperthermia to radiation compared with radiation alone.[276] No differences in overall survival have been shown. Delivery of local hyperthermia is technically demanding and requires specialized expertise and equipment (e.g., for monitoring temperatures and managing possible tissue burns). Therefore, the panel recommends hyperthermia use be limited to treatment centers with appropriate training, expertise, and equipment. The addition of hyperthermia generated substantial discussion and controversy among the panel and is a category 3 recommendation.

Systemic Disease

The systemic treatment of breast cancer recurrence or stage IV disease prolongs survival and enhances quality of life but is not curative. Therefore, treatments associated with minimal toxicity are preferred. Thus, minimally toxic endocrine therapies are preferred to cytotoxic therapy whenever reasonable.[278]

Guideline Stratification for Therapy in Systemic Disease: Patients with recurrent or metastatic breast cancer at diagnosis are initially stratified according to whether bone metastasis is present (see next section). These 2 patient subsets are then stratified further according to tumor hormone receptor and HER2 status (see page 154).

Supportive Therapy for Bone Metastasis: Treatment targeting osteoclast activity is of value in patients with metastatic breast cancer in bone to prevent bone fractures, bone pain requiring radiation therapy, spinal cord compression, and hypercalcemia (skeletal related events [SREs]).[279–281] The bisphosphonates zoledronic acid or pamidronate have been used for this purpose, and extensive clinical trial data support their efficacy in preventing SREs (see Bisphosphonates, facing page).

Recently, a single randomized, active controlled trial in metastatic breast cancer met the primary end point of equivalency and achieved a secondary end point of superior time to SRE occurrence with denosumab, a fully human monoclonal antibody directed against receptor activator of nuclear factor κ B (RANK) ligand, a mediator of osteoclast function,[282] compared with zoledronic acid.[281] Therefore, denosumab seems to be at least as efficacious as zoledronic acid in preventing SREs. No study of bisphosphonates or denosumab has been shown to affect overall survival in patients with metastatic disease.

The bisphosphonates and denosumab are associated with the occurrence of osteonecrosis of the jaw. Poor baseline dental health or requiring dental procedures during treatment are known risk factors for osteonecrosis of the jaw. Thus, a dental examination with preventive intervention is recommended before treatment with intravenous bisphosphonate or denosumab, and dental procedures during treatment should be avoided if possible. Additional risk factors for the development of osteonecrosis of the jaw include administration of chemotherapy or corticosteroids and poor oral hygiene with periodontal disease and dental abscess.[283]

Confirmation of metastatic disease through imaging, including radiograph, CT, or MRI, and initial evaluation of serum calcium, creatinine, phosphorous, and magnesium levels should be undertaken before initiation of intravenous bisphosphonate

treatment or subcutaneous denosumab treatment in patients with metastatic disease. Frequent measurement of calcium, phosphorous, and magnesium may be prudent because hypophosphatemia and hypocalcemia have been reported.

Bisphosphonates: Women with bone metastasis, especially if lytic, can be given a bisphosphonate (e.g., pamidronate, zoledronic acid) in combination with calcium citrate and vitamin D if expected survival is 3 months or longer and creatinine levels are below 3.0 mg/dL (category 1).[280,284–289] Bisphosphonates are given in addition to chemotherapy or endocrine therapy. Zoledronic acid may be superior to pamidronate in lytic breast metastasis.[290,291]

Use of bisphosphonates in patients with metastatic disease to bone is supported by extensive data from randomized clinical trials, including the use of zoledronic acid and pamidronate in the United States and ibandronate and clodronate in European countries.[287,289,291–296] In metastatic bone disease, bisphosphonate treatment is associated with fewer SREs and pathologic fractures, and less need for radiation therapy and surgery to treat bone pain.

Bisphosphonate use in metastatic disease is a palliative care measure. No impact on overall survival has been observed in patients treated with bisphosphonates. Data indicate that zoledronic acid and pamidronate may be given on a 3- to 5-weekly schedule in conjunction with antineoplastic therapy (e.g., endocrine therapy, chemotherapy, biologic therapy). Bisphosphonate use should be accompanied by calcium and vitamin D supplementation with daily doses of 1200 to 1500 mg of calcium and 400 to 800 IU of vitamin D_3. Recommended agents in the United States are pamidronate, 90 mg, intravenously over 2 hours or zoledronic acid, 4 mg, intravenously over 15 minutes. The original studies continued treatment for up to 24 months; however, limited long-term safety data indicate that treatment can continue beyond that time.[294,296,297] The risk of renal toxicity necessitates monitoring of serum creatinine before each dose is administered, and dose reduction or discontinuation if renal function is reduced. Current clinical trial results support the use of bisphosphonates for up to 2 years. Longer durations of bisphosphonate therapy may provide additional benefit, but this has not been tested in clinical trials.

Osteonecrosis of the jaw is a recently reported complication of bisphosphonate treatment. A review of more than 16,000 cancer patients documented an increased risk of jaw or facial bone surgery, and an increased risk of inflammatory conditions or osteomyelitis of the jaw associated with the use of intravenous bisphosphonates. An absolute risk of 5.48 events was seen per 100 patients treated, with an increased risk associated with increased cumulative drug dose.[298]

Denosumab: Based on the results of a single randomized trial comparing denosumab with zoledronic acid, women with metastatic breast cancer to bone who are candidates for bisphosphonate therapy may also be considered for denosumab treatment.[281] All trial patients were recommended to supplement with vitamin D and calcium. Patients on the experimental arm were given 120 mg of denosumab injected subcutaneously every 4 weeks plus intravenous placebo, compared with the control arm in which patients were given an intravenous infusion of 4 mg of zoledronic acid every 4 weeks plus subcutaneous placebo. In this trial with noninferiority as the primary end point, denosumab was shown to significantly delay time to first SRE by 18% compared with zoledronic acid (HR, 0.82; 95% CI, 0.71–0.95; $P < .001$ for noninferiority and $P = .01$ for superiority). No difference in time to progression or overall survival was observed. Adverse event profiles were similar between the groups, including incidence of osteonecrosis of the jaw, with a reduced risk of renal-related and acute-phase adverse events in the denosumab treatment group. Long-term risks of denosumab treatment are unknown, as is the optimal duration of treatment.

Endocrine Therapy: Women with recurrent or metastatic disease characterized by tumors that are ER- and/or PR-positive are appropriate candidates for initial endocrine therapy (see page 155). In postmenopausal women who have undergone previous antiestrogen therapy and are within 1 year of antiestrogen exposure, evidence supports the use of a selective aromatase inhibitor as the preferred first-line therapy for their recurrent disease.[299,300] For postmenopausal women who are antiestrogen-naive or are more than 1 year from previous antiestrogen therapy, aromatase inhibitors seem to have superior outcome compared with tamoxifen, although the differences are modest.[301–304] A recent Cochrane review also suggested a survival benefit favoring aromatase inhibitors over other endocrine therapies, although

the advantage is small.[305] A randomized phase III trial comparing tamoxifen and exemestane as first-line endocrine therapy for postmenopausal women with metastatic breast cancer showed no significant differences in progression-free or overall survival between the arms.[303] Therefore, either tamoxifen or an aromatase inhibitor is an appropriate option in this setting.

In premenopausal women with previous antiestrogen therapy who are within 1 year of antiestrogen exposure, the preferred second-line therapy is either surgical or radiotherapeutic oophorectomy or leuteinizing hormone–releasing hormone (LHRH) agonists with endocrine therapy, as it is for postmenopausal women. In premenopausal women without previous exposure to an antiestrogen, initial treatment is with an antiestrogen alone, or ovarian suppression or ablation plus endocrine therapy, as it is for postmenopausal women[306] (see page 155).

Limited studies document a progression-free survival advantage associated with adding trastuzumab or lapatinib to aromatase inhibition in postmenopausal women with hormone receptor–positive metastatic breast cancer.[307,308]

Many premenopausal and postmenopausal women with hormone-responsive breast cancer benefit from sequential use of endocrine therapies at disease progression. Therefore, women whose breast cancers respond to an endocrine maneuver with either shrinkage of the tumor or long-term disease stabilization (clinical benefit) should undergo additional endocrine therapy at disease progression (see page 158). Additional endocrine therapies for second-line and subsequent therapy are listed in the endocrine algorithm (see page 171).

The antiestrogen fulvestrant is an option for treating postmenopausal women with hormone receptor–positive metastatic breast cancer previously treated with an antiestrogen or an aromatase inhibitor. Fulvestrant lacks the estrogen agonistic activity of tamoxifen and is well tolerated as a single monthly gluteal intramuscular injection. Fulvestrant seems to be at least as effective as anastrozole in patients whose disease progressed on previous tamoxifen,[309,310] and a reanalysis of these studies suggests a longer duration of response favoring fulvestrant.[311] A phase II study of fulvestrant in postmenopausal women with advanced breast cancer and disease progression after aromatase inhibitor therapy documented a partial response rate of 14.3%, with an additional 20.8% of patients experiencing stable disease for at least 6 months.[312] Furthermore, in a phase III trial of postmenopausal women with hormone receptor–positive advanced breast cancer who experienced disease progression on prior nonsteroidal aromatase inhibitor therapy showed that exemestane and fulvestrant had comparable clinical benefit rates (32.2% vs. 31.5%; $P = .853$).[313] In that study, fulvestrant was administered as a 500-mg loading dose followed by doses of 250 mg on day 14 and 28, and then monthly. A pharmacokinetic analysis showed that steady-state levels of the drug were achieved earlier than with the FDA-approved standard dosing regimen of 250 mg monthly.[314] The panel considers both this loading-dose regimen and the FDA-approved regimen to be appropriate for administration of fulvestrant.

Endocrine therapies in postmenopausal women include selective, nonsteroidal aromatase inhibitors (anastrozole and letrozole); steroidal aromatase inhibitors (exemestane); pure antiestrogens (fulvestrant); progestin (megestrol acetate); androgens (fluoxymesterone); and high-dose estrogen (ethinyl estradiol). In premenopausal women, therapies include LHRH agonists (goserelin and luprolide); surgical or radiotherapeutic oophorectomy; progestin (megestrol acetate); androgens (fluoxymesterone); and high-dose estrogen (ethinyl estradiol). After second-line endocrine therapy, little high-level evidence exists to help select the optimal sequence of endocrine therapy.

Endocrine therapy may be effective in patients with negative ER and PR determinations, especially on the primary tumor and in soft tissue disease and/or bone-dominant disease.[315–317] Endocrine therapy is also associated with relatively low toxicity. Furthermore, false-negative determinations of ER and PR tumor status are not unusual, and the hormone receptor status of primary and metastatic sites of disease may differ. The panel recommends a trial of endocrine therapy be considered in patients with disease characterized as hormone receptor–negative or hormone receptor–positive and endocrine-refractory and localized to the bone or soft tissue only or is associated with asymptomatic visceral disease, irrespective of HER2 tumor status (see pages 156 and 157).

Cytotoxic Chemotherapy: Women with hormone receptor–negative tumors not localized to the bone or soft tissue only or that are associated with symptomatic visceral metastasis, or who have hormone

receptor–positive tumors that are refractory to endocrine therapy, should undergo chemotherapy (see pages 156 and 157). Various chemotherapy regimens believed to be appropriate are outlined in the treatment algorithm (see pages 172–177). Combination chemotherapy generally provides higher rates of objective response and longer time to progression than single-agent chemotherapy. Combination chemotherapy is, however, associated with an increase in toxicity, and has little survival benefit.[318–321] Furthermore, administering single agents sequentially decreases the likelihood that dose reductions will be needed. Thus, the panel finds little compelling evidence that combination chemotherapy is superior to sequential single agents. Standard clinical practice is to continue first-line chemotherapy until disease progression, although adverse effects may require dose reduction and cessation of chemotherapy before disease progression occurs. Limited information suggests that progression-free survival can be prolonged with continuous chemotherapy versus shorter-course chemotherapy,[322,323] but because of the lack of differences in overall survival, the benefits of continuous chemotherapy must be weighed against its detrimental effects on overall quality of life.

Single cytotoxic agents and combination chemotherapy regimens recommended by the panel for the treatment of patients with metastatic disease are listed on page 172–177. Single agents are categorized as either *preferred* or *other* based on a balance of the efficacy, toxicity, and treatment schedules of the drugs. Combination regimens are also categorized as either *preferred* or *other*.

Preferred chemotherapies thus include sequential single agents or combination chemotherapy. Among preferred first-line single agents, the panel includes the anthracyclines (doxorubicin, epirubicin, and pegylated liposomal doxorubicin); the taxanes (paclitaxel, docetaxel, and albumin-bound paclitaxel); anti-metabolites (capecitabine and gemcitabine); and nontaxane microtubule inhibitors (eribulin and vinorelbine). Among preferred first-line combination regimens, the panel includes FAC/CAF, FEC, AC, EC, AT, CMF, docetaxel and capecitabine, and gemcitabine and paclitaxel. Under the heading of other single agents are cyclophosphamide, cisplatin, oral etoposide (category 2B), vinblastine, mitoxantrone, ixabepilone, and fluorouracil (by continuous infusion). As with endocrine therapy, sequential responses are often observed with chemotherapy, supporting the use of sequential single agents and combination chemotherapy regimens. The current guidelines include doses and schedules of these single agents and combination regimens for metastatic breast cancer (see pages 172–177).

A series of recent trials have sought to define the role for bevacizumab, a humanized monoclonal antibody against the vascular endothelial growth factor (VEGF), in the treatment of metastatic breast cancer. The E2100 trial randomized 722 women with recurrent or metastatic breast cancer to first-line chemotherapy with paclitaxel with or without bevacizumab.[324] This trial documented superior progression-free survival (11.8 vs. 5.9 months; HR, 0.60; $P < .001$) favoring bevacizumab plus paclitaxel compared with paclitaxel alone. A similar trial (Avastin and Docetaxel [AVADO])[325] randomized 736 patients to treatment with either docetaxel and bevacizumab, or docetaxel and placebo. This trial also documented increased progression-free survival in the arm containing bevacizumab (10.1 vs. 8.2 months with docetaxel alone; HR, 0.77; $P = .006$). An additional trial, RIBBON-1, randomized patients to either bevacizumab in combination with chemotherapy consisting of either capecitabine, docetaxel, nab-paclitaxel, or FEC/CAF/AC/EC, or each chemotherapy alone. Results of this trial show a statistically significant increase in progression-free survival in patients treated with bevacizumab and capecitabine (8.6 vs. 5.7 months; HR, 0.688; $P = .0002$) and taxane or anthracycline (9.2 vs. 8.0 months; HR, 0.644; $P < .0001$).[326]

None of these studies show an increase in overall survival or quality of life when analyzed alone or in a meta-analysis combining the trials.[327] The increase in progression-free survival with bevacizumab is modest, and appears the greatest in combination with paclitaxel, especially as reported in an unpublished analysis provided to the FDA.[328]

Eribulin is a nontaxane microtubule inhibitor approved by the FDA in November 2010 for the treatment of patients with metastatic breast cancer who previously received at least 2 chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting. A phase III study of eribulin versus treatment of physicians choice in heavily pretreated patients with

metastatic breast cancer showed an improved overall survival of approximately 2.5 months for those on the eribulin arm (HR, 0.81; 95% CI, 0.66–0.99; P = .041). No difference in time to progression was observed (HR, 0.87; 95% CI, 0.71–1.05; P = .14).[329]

Ixabepilone, an epothilone B analogue, is a newer agent for treatment of recurrent or metastatic breast cancer either as a single agent (category 2A) or in combination with capecitabine (category 2B), listed in *other active options* groups (see pages 172–177). Several phase II trials have evaluated ixabepilone as monotherapy in women with metastatic breast cancer: in a first-line setting in patients previously treated with anthracycline chemotherapy,[330] in patients with taxane-resistant metastatic breast cancer,[331] and in patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine.[332] In the phase II trials, objective response rate, median duration of response, and median overall survival were 41.5% (95% CI, 29.4%–54.4%), 8.2 months (95% CI, 5.7–10.2 months), and 22.0 months (95% CI, 15.6–27.0 months), respectively, in the first-line setting[330]; 12% (95% CI, 4.7%–26.5%), 10.4 months, and 7.9 months, respectively for the taxane-resistant patients[331]; and 11.5% (95% CI, 6.3%–18.9%), 5.7 months, and 8.6 months, respectively for the patients previously treated with an anthracycline, a taxane, and capecitabine.[332] In the study by Perez et al.,[332] grade 3/4 treatment-related toxicities included peripheral sensory neuropathy (14%) and neutropenia (54%). In addition, a phase III study compared ixabepilone plus capecitabine with capecitabine alone in women with metastatic breast cancer that progressed after anthracycline and taxane treatment.[333] The primary end point of progression-free survival was 5.8 versus 4.2 months (HR, 0.75; 95% CI, 0.64–0.88; P = .0003), respectively, and the objective response rate was 35% versus 14% (P < .0001), respectively. No data on overall survival were reported, although the incidence of treatment-related death resulting from neutropenia was substantially higher in the combination arm.

A tumor's failure to respond to 3 sequential chemotherapy regimens or an ECOG performance status of 3 or greater is an indication for supportive therapy only. In this context, failure of the tumor to respond to a chemotherapy regimen means the absence of even a marginal response to a given chemotherapy regimen. Response to a chemotherapy regimen followed by disease progression is not considered a failed response.

Patients with metastatic breast cancer frequently develop several anatomically localized problems that may benefit from local irradiation, surgery, or regional chemotherapy (e.g., intrathecal methotrexate for leptomeningeal carcinomatosis).

HER2-Targeted Therapy: Patients with tumors that are HER2-positive may derive benefit from treatment with trastuzumab as a single agent or in combination with selected chemotherapeutic agents. Those refractory to therapy with an anthracycline, a taxane, and trastuzumab may derive benefit from the combination of capecitabine plus lapatinib (see page 157). The panel recommends selecting patients for HER2-targeted therapy if their tumors are either positive for HER2 according to FISH or 3+ according to immunohistochemistry. HER2 testing recommendations are described in the guidelines (see page 159). Patients with tumors with immunohistochemistry scores of 0 or 1+ for HER2 or FISH non-amplified results have very low rates of HER2-targeted response, and therapy with trastuzumab or lapatinib is not warranted.[334] Adequate standardization and validation of HER2 assays with FISH and immunohistochemistry used in clinical practice is a concern, and data suggest that false-positive determinations are common.[20,22,25,26,335] Recommendations regarding HER2 testing have been published.[25,26]

First-line trastuzumab in combination with selected chemotherapeutics[156] or as a single agent[155,157] is recommended in patients with metastatic breast cancer with HER2-positive tumors that are hormone receptor–negative (see pages 172–177). Randomized trials show benefit from adding trastuzumab to other agents, including paclitaxel with or without carboplatin,[156,334,336,337] docetaxel,[336] and vinorelbine,[336] or as a single agent[157] for patients with HER2-positive disease. In addition, the combination of trastuzumab and capecitabine has also shown efficacy as a first-line trastuzumab-containing regimen in this population of patients.[338,339] For patients with hormone receptor–positive, HER2-positive disease, the panel recommends initial treatment with endocrine therapy, an approach consistent with most of these studies. The panel believes the 27% frequency of significant cardiac dysfunction in patients treated with the combination of trastuzumab and doxorubicin/

cyclophosphamide chemotherapy in the metastatic setting is too high to use this combination outside of a prospective clinical trial.[156,339,340]

The panel recommends continuing HER2 blockade for patients with HER2-positive metastatic breast cancer that progresses on first-line trastuzumab-containing regimens. This recommendation also applies to the relatively new class of patients who are diagnosed with HER2-positive metastatic disease following prior exposure to trastuzumab in the adjuvant setting. Several recent trials have shown benefit of continuing trastuzumab therapy after disease progression on a trastuzumab-containing regimen.[341–343] However, the optimal duration of trastuzumab in patients with long-term control of disease is unknown. The regimen of capecitabine plus lapatinib is also an option for patients with HER2-positive disease after progression on a trastuzumab-containing regimen.

A phase III study compared lapatinib plus capecitabine with capecitabine alone in women with advanced or metastatic breast cancer refractory to trastuzumab in the metastatic setting and who underwent prior treatment with an anthracycline and a taxane in either the metastatic or adjuvant setting.[344] Time to progression was increased in the group undergoing combination therapy compared with the group receiving capecitabine monotherapy (8.4 vs. 4.4 months; HR, 0.49; 95% CI, 0.34–0.71; $P < .001$). Another study of women with metastatic breast cancer showed that lapatinib in combination with letrozole increased progression-free survival over letrozole alone in the subset of women with HER2-positive cancer (3.0 months for letrozole and placebo vs. 8.2 months for letrozole and lapatinib; HR, 0.71; 95% CI, 0.53–0.96; $P = .019$).[307] In addition, results from a phase III trial in which patients with heavily pretreated metastatic breast cancer and disease progression on trastuzumab therapy were randomly assigned to monotherapy with lapatinib or trastuzumab plus lapatinib showed that progression-free survival was increased from 8.1 to 12 weeks ($P = .008$) with the combination.[345,346] The current NCCN Guidelines include doses and schedules of representative chemotherapy single agents and regimens for use in combination with either trastuzumab or lapatinib for metastatic breast cancer, and for the combination of lapatinib and trastuzumab (see pages 172–177). Based on the lack of data, the panel does not recommend adding chemotherapy to the trastuzumab/lapatinib combination. The optimal duration of HER2-targeted therapy in patients with long-term disease control is unknown.

Surgery: The panel recommends systemic therapy as the primary treatment approach for women with metastatic breast cancer and an intact primary tumor, with consideration of surgery after initial systemic treatment for those requiring palliation of symptoms or with impending complications, such as skin ulceration, bleeding, fungation, and pain.[347] Generally this surgery should be undertaken only if complete local clearance of tumor may be obtained and if other sites of disease are not immediately life-threatening. Alternatively, radiation therapy may be considered. Often, surgery requires collaboration between the breast and reconstructive surgeons to provide optimal cancer control and wound closure.

Recent retrospective studies suggest a potential survival benefit from complete excision of the in-breast tumor in select patients with metastatic breast cancer.[348–351] Substantial selection biases exist in all of these studies and are likely to confound the study results.[352,353] Nevertheless, the panel recognizes the need for randomized clinical trials that will address the risks and benefits of local therapy for patients with stage IV disease while eliminating selection biases. Patient enrollment in these trials is encouraged.

Special Situations

Information on Paget's disease, phyllodes tumors and breast cancer during pregnancy can be found in the full NCCN Guidelines for Breast Cancer available at www.NCCN.org. The treatment algorithm for inflammatory breast cancer can also be found online at www.NCCN.org.

Inflammatory Breast Cancer: Inflammatory breast cancer (IBC) is a rare, aggressive form of breast cancer estimated to account for 1% to 6% of breast cancer cases in the United States.[354,355] IBC is a clinical diagnosis that requires erythema and dermal edema (peau d'orange) of a third or more of the skin of the breast with a palpable border to the erythema. IBC is classified according to the 7th edition of the *AJCC Cancer Staging Manual* as stage IIIB, IIIC, or IV breast cancer, depending on the degree of nodal involvement and whether distant metastases are present. The primary tumor of IBC is classified as T4d by definition, even when no mass is specifically apparent in the breast. On radiographic imaging, skin thickening and, in

some cases, an underlying mass are observed. Despite use of the term *inflammatory*, the characteristic clinical features of IBC are caused by blockage of dermal lymphatics by tumor emboli. Although a biopsy is required to evaluate for the presence of cancer in breast tissue and the dermal lymphatics, a diagnosis of IBC is based on clinical findings, and dermal lymphatic involvement is neither required nor sufficient alone to diagnose IBC.[356,357] The differential diagnosis includes cellulitis of the breast and mastitis.

In the past, IBC has often been placed under the general heading of locally advanced breast cancer. Increasing evidence shows that patients with IBC are more likely to have disease that is HER2-positive and hormone receptor–negative,[358,359] to have a less favorable prognosis[360,361](i.e., disease-free survival at 5 years was 35% and 50% for inflammatory vs. noninflammatory status, respectively; $P = .020$[362]), and to be younger at disease presentation than those with noninflammatory forms of locally advanced breast cancer.[363] The panel acknowledges that studies focusing on genetic characterization of IBC are needed to more clearly define IBC as a disease entity and to optimize treatment.[364,365] Nevertheless, current evidence provides justification for a separate guideline for the workup and treatment of patients diagnosed with IBC (see page IBC-1; available online, in these guidelines, at www.NCCN.org).

Women with a clinical/pathologic diagnosis of IBC without distant metastasis (stage T4d, N0–N3, M0) should undergo a thorough staging evaluation. Recommendations include a complete history and physical examination, complete blood cell count, and platelet count. Evaluations for the presence of distant metastasis include liver function testing, bone scan (category 2B), and CT imaging of the chest, abdomen, and pelvis (category 2B; category 2A for CT imaging of the chest when pulmonary symptoms are present). Extent of local disease is determined using diagnostic bilateral mammogram, with the addition of ultrasound as necessary. A breast MRI scan is optional. A pathology review and prechemotherapy determinations of tumor hormone-receptor and HER2-receptor status should be performed. Genetic counseling is recommended if the patient is considered to be at high risk of 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). PET/CT scan is also included as an optional additional study (category 2B). Panel consensus is that PET/CT is most helpful when standard imaging results are equivocal or suspicious. However, limited evidence suggests that PET/CT may be a useful adjunct to standard imaging in the setting of IBC because of the increased risk of regional lymph node involvement and distant spread of disease in this group of patients.[40,41,366,367] Nevertheless, equivocal or suspicious sites identified by PET/CT scanning or other imaging methods should be biopsied for confirmation of stage IV disease whenever possible.

The treatment of patients with IBC should involve a combined modality approach.[354] The benefit of preoperative chemotherapy followed by mastectomy over preoperative chemotherapy alone in patients with IBC was shown in a retrospective analysis in which lower local recurrence rates and longer disease-specific survival were reported for the combined modality approach.[368] Results from a retrospective study of patients with IBC performed over a 20-year period at MD Anderson Cancer Center showed that initial treatment with doxorubicin-based chemotherapy followed by local therapy (e.g., radiation therapy or mastectomy, or both) and additional postoperative chemotherapy resulted in a 15-year disease-free survival rate of 28%.[369] Additional support for the use of anthracycline-based preoperative chemotherapy comes from the only randomized trial of patients with IBC. In this study, 5-year survival rates of 44% were observed when epirubicin/cyclophosphamide-based regimens were administered as initial therapy.[370] A recent retrospective study showed that the addition of a taxane to an anthracycline-based regimen improved progression-free and overall survival in patients with ER-negative IBC.[371] A recent systematic review found evidence for an association between the intensity of preoperative therapy and the likelihood of a pathologic complete response.[372]

It has been known for many years that primary surgical treatment of patients with IBC is associated with very poor outcomes.[373] Breast-conserving surgery in patients with IBC has been associated with poor cosmesis, and limited data suggest that rates of local recurrence may be higher than with mastectomy.

The panel recommends preoperative chemotherapy with an anthracycline-based regimen with or without taxanes for the initial treatment of pa-

tients with IBC (see page IBC-1; available online, in these guidelines, at www.NCCN.org). Inclusion of trastuzumab in the chemotherapy regimen is recommended for patients with HER2-positive disease. Patients with a clinical/pathologic diagnosis of IBC should not be treated with prechemotherapy surgery. Patients whose disease responds to preoperative chemotherapy should undergo mastectomy with axillary lymph node dissection; breast-conserving therapy is not recommended for those with IBC. Any remaining planned chemotherapy should be completed postmastectomy followed sequentially by endocrine therapy in patients with hormone receptor–positive disease. If the IBC is HER2-positive, completion of 1 year of trastuzumab is recommended. Finally, postmastectomy chest wall and regional node irradiation is recommended after completion of any planned chemotherapy (see page IBC-1; available online, in these guidelines, at www.NCCN.org). Mastectomy is not recommended for patients with IBC whose disease does not respond to preoperative chemotherapy. Additional systemic chemotherapy and/or preoperative radiation should be considered for these patients, and those responding to this secondary therapy should undergo mastectomy and subsequent treatment as described earlier. Patients with stage IV or recurrent IBC should be treated according to the guidelines for recurrence/stage IV disease (see pages 153 to 160).

Axillary Breast Cancer: Axillary metastasis from an occult breast cancer represents 3% to 5% of breast cancers. Evidence supporting recommendations for management of these patients comes from a limited number of retrospective studies involving small numbers of patients[374–376] (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.[375,376]

Some evidence indicates that MRI of the breast can facilitate identification of occult breast cancer, and help select those 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% of the patients.[375] 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 seen at a median follow-up of 19 months.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Occult 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 of these guidelines, 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 for 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 T0N1M0 disease, options include either mastectomy plus axillary nodal dissection or axillary nodal dissection plus whole breast irradiation with or without nodal irradiation (see page 161). Systemic chemotherapy, endocrine therapy, or trastuzumab is given according to the recommendations for stage II or III disease (see page 141). 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 page 151).

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 NCCN

Guidelines are based on the results of past and present clinical trials. However, not a 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.

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Individual Disclosures for the NCCN Invasive Breast Cancer Panel

Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
D. Craig Allred, MD	None	None	Clarient, Inc.	None	1/15/10
Benjamin O. Anderson, MD	General Electric; GlaxoSmithKline; and sanofi-aventis U.S.	Wyeth Pharmaceuticals	None	None	7/18/10
Harold J. Burstein, MD, PhD	None	None	None	None	10/29/09
Robert W. Carlson, MD	AstraZeneca Pharmaceuticals LP; Genentech, Inc.; and sanofi-aventis U.S.	Amgen Inc.; Genentech, Inc.; and Pfizer Inc.	None	None	11/29/10
W. Bradford Carter, MD	None	None	None	None	12/2/09
Stephen B. Edge, MD	None	None	None	None	11/5/10
John K. Erban, MD	None	Macrogenics; and Transmolecular, Inc.	None	None	7/22/09
William B. Farrar, MD	None	None	None	None	10/29/09
Andres Forero, MD	Biogen Idec; Daiichi- Sankyo Co.; Eli Lilly and Company; Genentech, Inc.; BioCryst; Immunomedics; and Seattle Genetics	None	None	None	9/28/09
Sharon Hermes Giordano, MD, MPH	None	None	None	None	11/3/09
Lori J. Goldstein, MD	AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; Genomic Health, Inc.; GlaxoSmithKline; Merck & Co., Inc.; sanofi-aventis U.S.; and Wyeth Pharmaceuticals	Amgen Inc.; AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; Eisai Inc.; Eli Lilly and Company; Genentech, Inc.; Genomic Health, Inc.; GlaxoSmithKline; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Pharmion Corporation; Roche Laboratories, Inc.; and sanofi-aventis U.S.	None	None	11/4/09
William J. Gradishar, MD	None	Abraxis Bioscience, Inc.; Bayer HealthCare; Genentech, Inc.; General Electric; GlaxoSmithKline; Onyx Pharmaceuticals, Inc.; and sanofi-aventis U.S.	None	None	7/19/10
Daniel F. Hayes, MD	AstraZeneca Pharmaceuticals LP; GlaxoSmithKline; Novartis Pharmaceuticals Corporation; Pfizer Inc.; and Veridex, LLC	Chugai Pharmaceuticals; Compendia Bioscience; and DNAR (DNA Repair, Boston, MA)	Halcyon Diagnostics, Inc; and Oncimmune LLC	None	5/26/10
Clifford A. Hudis, MD	Merck & Co., Inc.; and Onyx Pharmaceuticals, Inc.	Bayer HealthCare; Boehringer Ingelheim GmbH; Eisai Inc.; Genentech, Inc.; and sanofi-aventis U.S.	None	None	9/22/10
Britt-Marie Ljung, MD	National Cancer Institute	Versant ventures	None	None	9/21/10
David A. Mankoff, MD, PhD	Merck & Co., Inc.; and Pfizer Inc.	Genzyme Corporation	None	None	7/1/10
P. Kelly Marcom, MD	Bristol-Myers Squibb Company; Genentech, Inc.; Novartis Pharmaceuticals Corporation; and DoD/CDMRP	AstraZeneca Pharmaceuticals LP; and Genentech, Inc.	None	None	12/16/09
Ingrid A. Mayer, MD	None	None	None	None	9/27/10
Beryl McCormick, MD	None	None	None	None	4/22/10
Lori J. Pierce, MD	None	None	None	None	8/4/09
Elizabeth C. Reed, MD	None	UnitedHealthcare	None	None	11/2/09
Jasgit Sachdev, MD	Abraxis Oncology; Genentech, Inc.; and Wyeth Pharmaceuticals	Genomic Health, Inc.; and GlaxoSmithKline	None	None	4/6/10
Mary Lou Smith, JD, MBA	None	Eli Lilly and Company	None	None	12/30/09
George Somlo, MD	American BioSciences Inc.; AstraZeneca Pharmaceuticals LP; National Cancer Institute; and Abraxane	Bristol-Myers Squibb Company; Genentech, Inc.; Novartis Pharmaceuticals Corporation; Abraxane; and Roche Laboratories, Inc.	None	None	11/2/09
John H. Ward, MD	None	None	None	None	12/27/10
Antonio C. Wolff, MD	Genentech, Inc.; and Roche Laboratories, Inc.	None	None	None	11/2/09
Richard Zellars, MD	None	None	None	None	1/11/11

The NCCN guidelines staff have no conflicts to disclose.