NCCN National Comprehensive Cancer Network®

The NCCN

Breast Cancer

Clinical Practice Guidelines in Oncology™

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Overview

The American Cancer Society estimated that 184,450 new cases of invasive breast cancer would be diagnosed and 40,930 patients would die of the disease in the United States in 2008.[1] In addition, approximately 67,770 women will be diagnosed with carcinoma in situ of the breast during the same year. Breast cancer is the

Breast Cancer Clinical Practice Guidelines in Oncology

Key Words

NCCN Clinical Practice Guidelines, breast cancer, chemotherapy, breast-conserving therapy, adjuvant therapy, mastectomy, endocrine therapy, radiation, therapy, lobular carcinoma in situ, ductal carcinoma in situ (*JNCCN* 2009;7:122–192)

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 Breast Cancer Clinical Practice Guidelines presented here are the work of the members of the NCCN Breast Cancer Clinical Practice Guidelines Panel. Categories of evidence were assessed and are noted on the algorithms and in the text. Although not explicitly stated at every decision point of the Guidelines, patient participation in prospective clinical trials is the preferred option of treatment for all stages of breast cancer. The full breast cancer guidelines are not printed in this issue of *JNCCN*, but can be accessed online at www.nccn.org.

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

Please Note

These 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 these 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 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 Breast Cancer Guidelines Panel

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 Breast Cancer Guidelines Panel members can be found on page 192. (To view the most recent version of these guidelines and accompanying disclosures, visit 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.

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 etiology of most breast cancer cases is unknown. However, numerous risk factors for the disease have been established, including female gender, increasing patient age, family history of breast cancer at a young age, early menarche, late menopause, older age at first live childbirth, prolonged hormone replacement therapy, previous exposure to therapeutic chest wall irradiation, benign proliferative breast disease, and genetic mutations, such as of the *BRCA1/2* genes. However, except for female gender and increasing patient age, these risk factors are associated with only few breast cancers. Women with a strong family history of breast cancer should be evaluated according to the NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian (to see the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org). Women at increased risk for breast cancer (generally those with a ≥ 1.67% 5-year risk using the Gail model of risk assessment[3]) may consider risk

Text continues on p. 157

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 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] Optional additional studies for breast imaging: • Breast MRI[c] Optional additional studies or as directed by symptoms for stage I (only in the presence of symptoms or other abnormal staging studies) or for stage IIA, IIB, and IIIA (T3, N1, M0)[d] • Bone scan indicated if localized symptoms or elevated alkaline phosphatase (category 2A) or if T3, N1, M0 (category 2B) • Abdominal ± pelvis CT, US, or MRI (indicated if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, abnormal physical examination of the abdomen or pelvis, or if T3, N1, M0) • Chest imaging (if pulmonary symptoms are present) • Genetic counseling if patient is high risk for hereditary breast cancer[e]

[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 141).
[c] See Principles of Dedicated Breast MRI Testing (page 142).
[d] The use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer.
[e] See NCCN Clinical Practice Guidelines in Oncology: Genetics/Familial High-Risk Assessment. To view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org.

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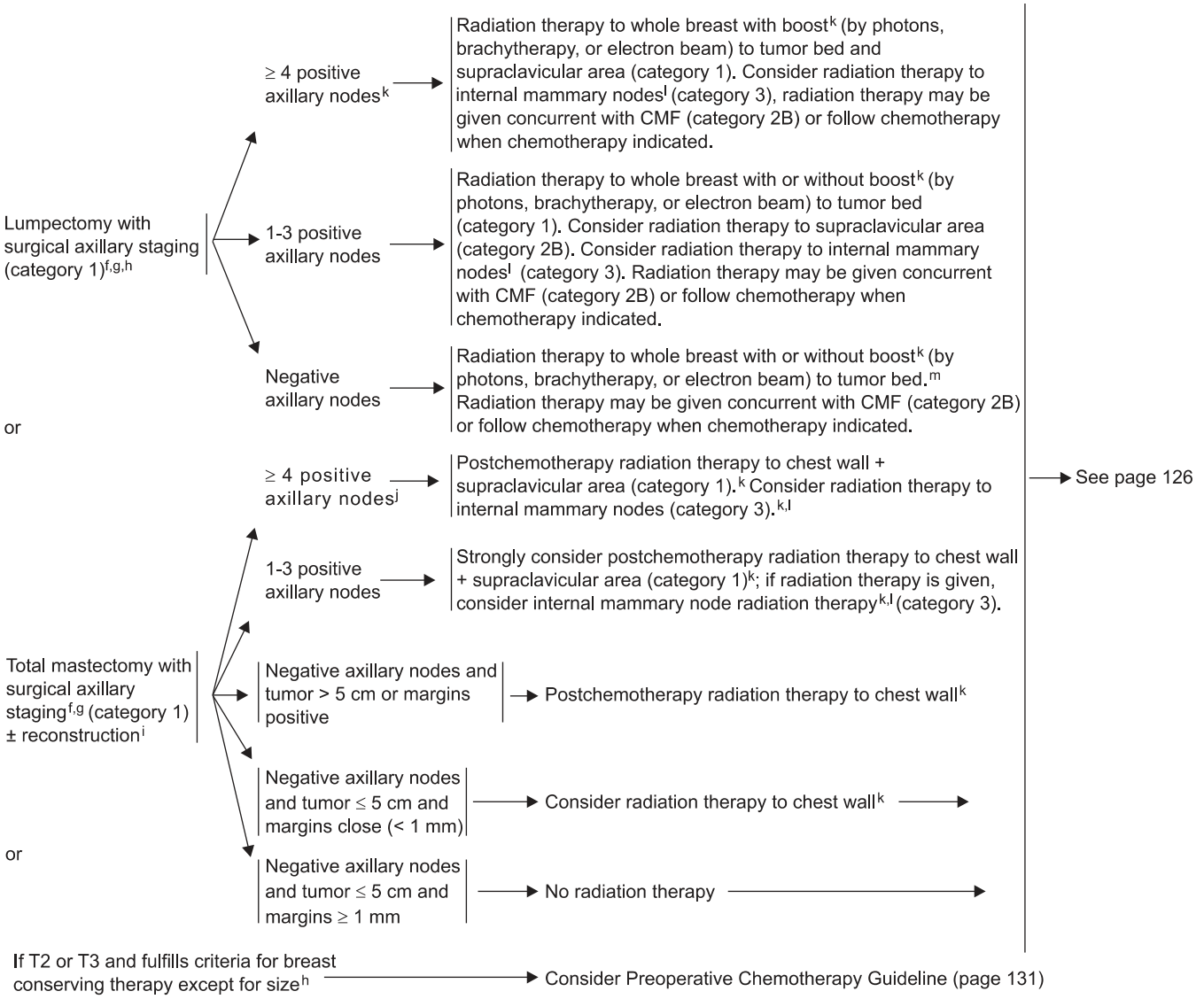
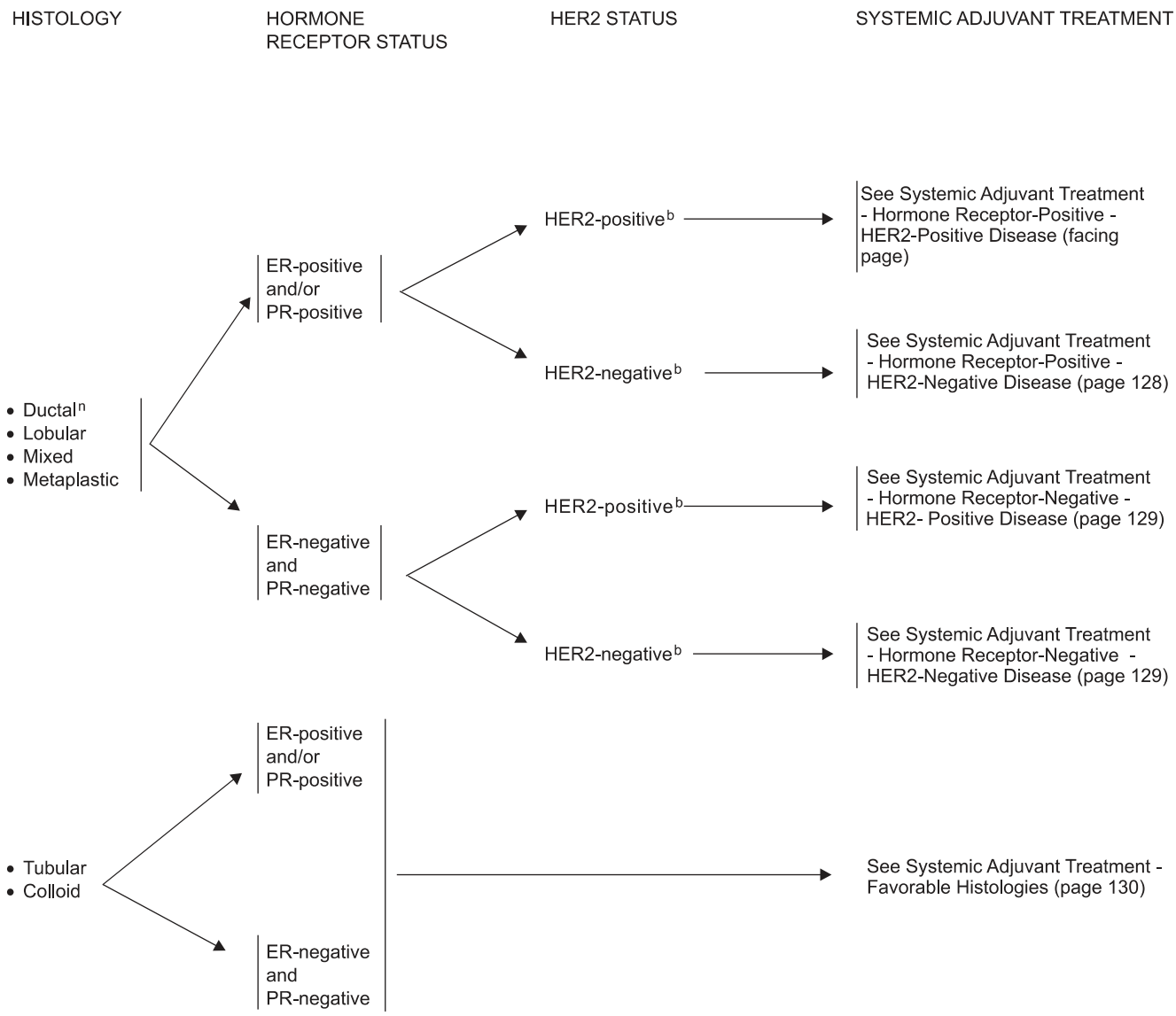
LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3, N1, M0



[f] See Surgical Axillary Staging (page 142).
[g] See Axillary Lymph Node Staging (page 143) and Margin Status in Infiltrating Carcinoma (page 143).
[h] See Special Considerations to Breast-Conserving Therapy Requiring Radiation Therapy (page 144).
[i] See Principles of Breast Reconstruction Following Surgery (page 144).
[j] Consideration may be given to additional staging including bone scan and abdominal CT/US/MRI; chest CT (category 2B).
[k] See Principles of Radiation Therapy (page 145).
[l] 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 utilized in all cases where radiation therapy is delivered to the internal mammary lymph nodes.
[m] Breast irradiation may be omitted in those aged 70 y or older with ER positive, clinically node-negative, T1 tumors who receive adjuvant endocrine therapy (category 1).



[b] See Principles of HER2 Testing (page 141)
[n] This includes medullary and micropapillary subtypes.

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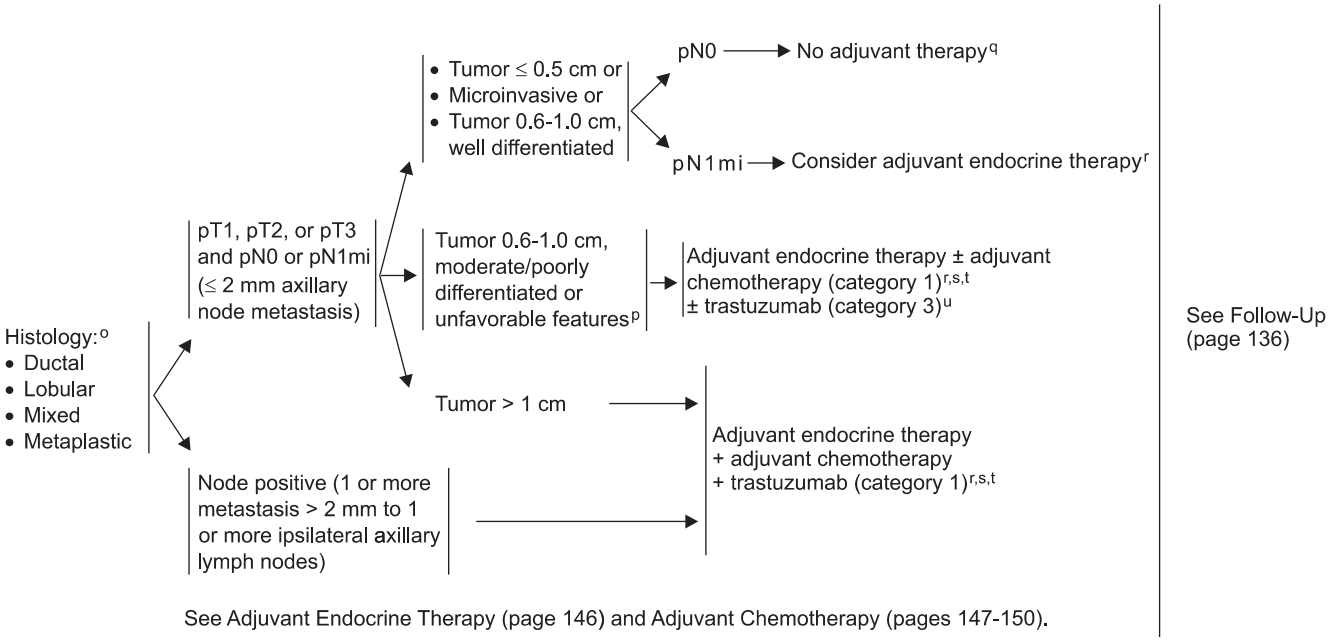
SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-POSITIVE - HER2 POSITIVE DISEASE[b]



See Adjuvant Endocrine Therapy (page 146) and Adjuvant Chemotherapy (pages 147-150).

[b] See Principles of HER2 Testing (page 141)

[o] 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.

[p] Unfavorable features: angiolymphatic invasion, high nuclear grade, or high histologic grade.

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

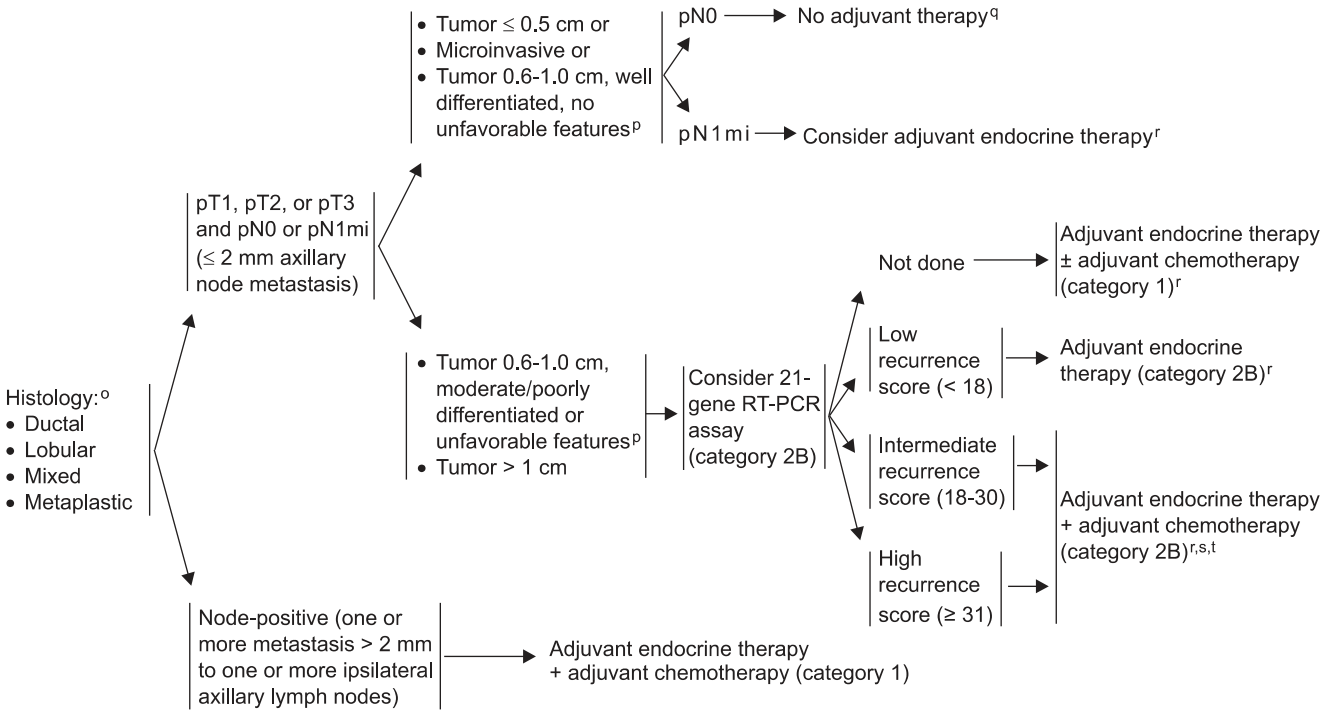
[r] Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. Early evidence suggests similar benefits from ovarian suppression (i.e., LHRH agonist) as from 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 received adjuvant chemotherapy is uncertain.

[s] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following 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 and women aged ≥ 60 y in whom the incremental benefit of chemotherapy may be smaller. Available data suggest sequential or concurrent endocrine therapy with radiation therapy is acceptable.

[t] Data are insufficient to make chemotherapy recommendations for patients > 70 y. Treatment should be individualized with consideration of comorbid conditions.

[u] 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 the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.

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



See Adjuvant Endocrine Therapy (page 146) and Adjuvant Chemotherapy (pages 147-150)

[b] See Principles of HER2 Testing (page 141).

[o] 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.

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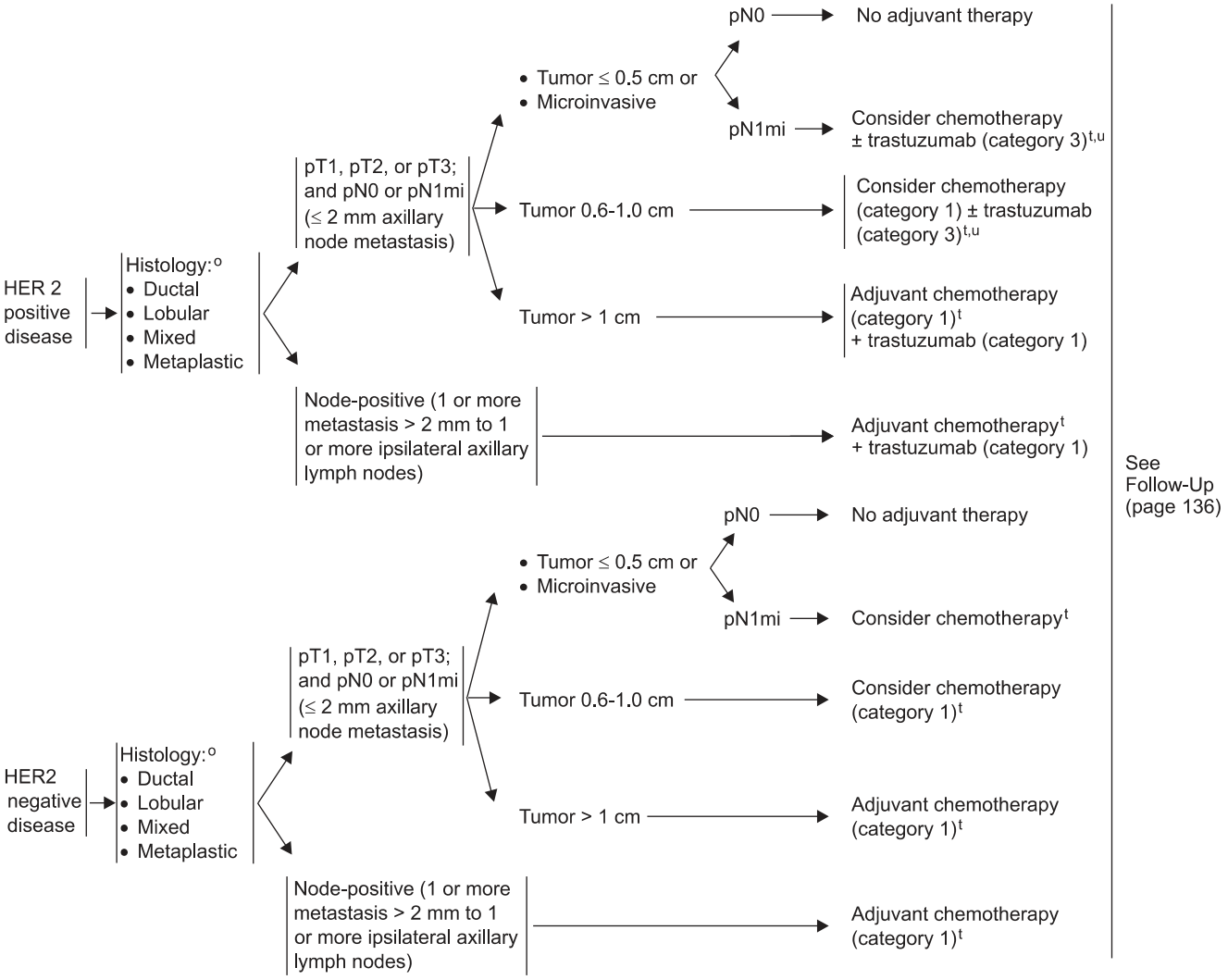
[t] Data are insufficient to make chemotherapy recommendations for patients > 70 y. Treatment should be individualized with consideration of comorbid conditions.

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



See Adjuvant Endocrine Therapy (page 146) and Adjuvant Chemotherapy (pages 147-150)

[b] See Principles of HER2 Testing (page 141).

[o] 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.

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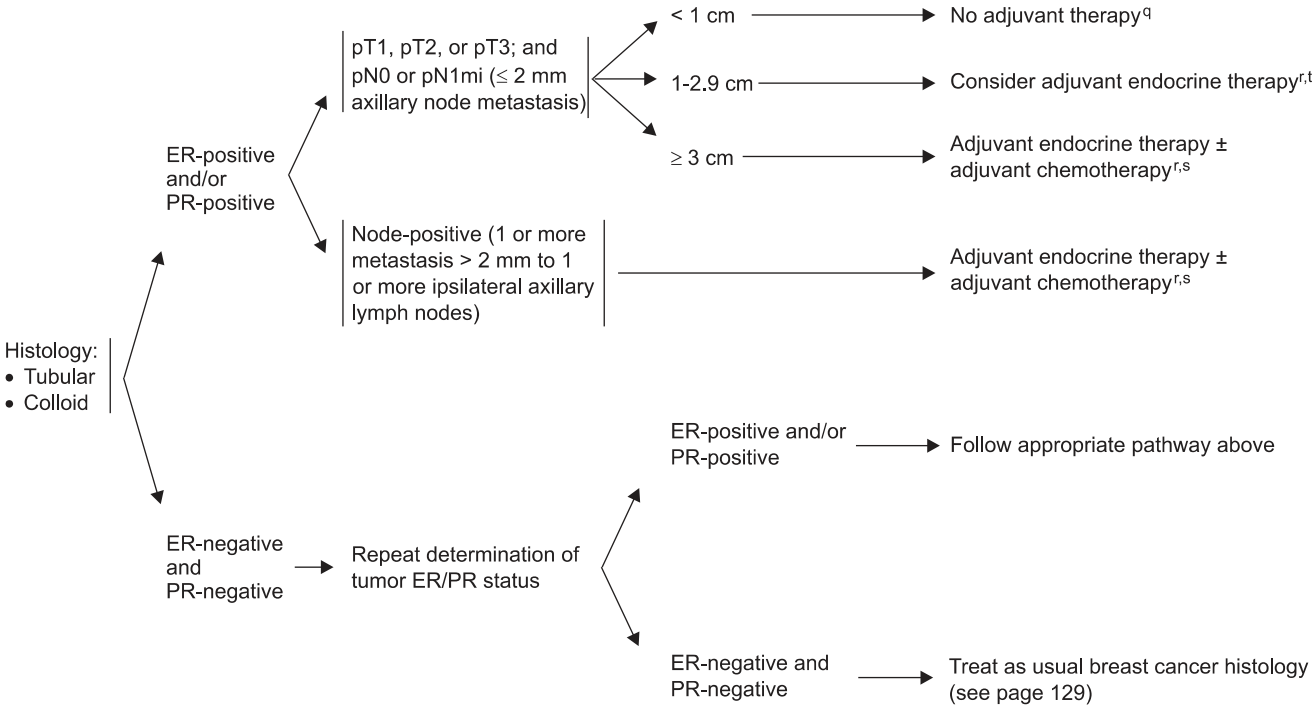
SYSTEMIC ADJUVANT TREATMENT - FAVORABLE HISTOLOGIES



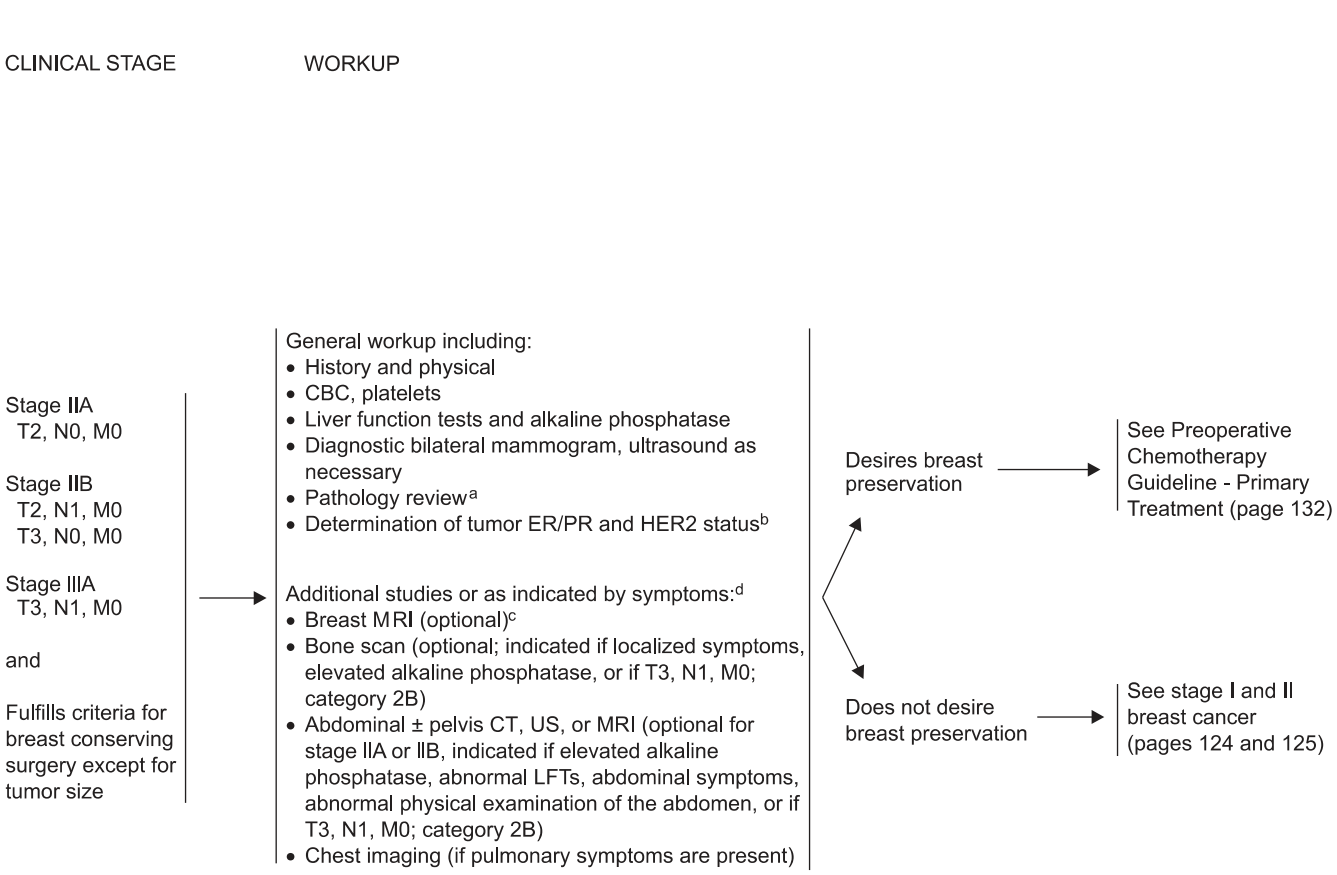
See Adjuvant Endocrine Therapy (page 146) and Adjuvant Chemotherapy (pages 147-150)

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

[r] 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., LHRH 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 received adjuvant chemotherapy is uncertain.

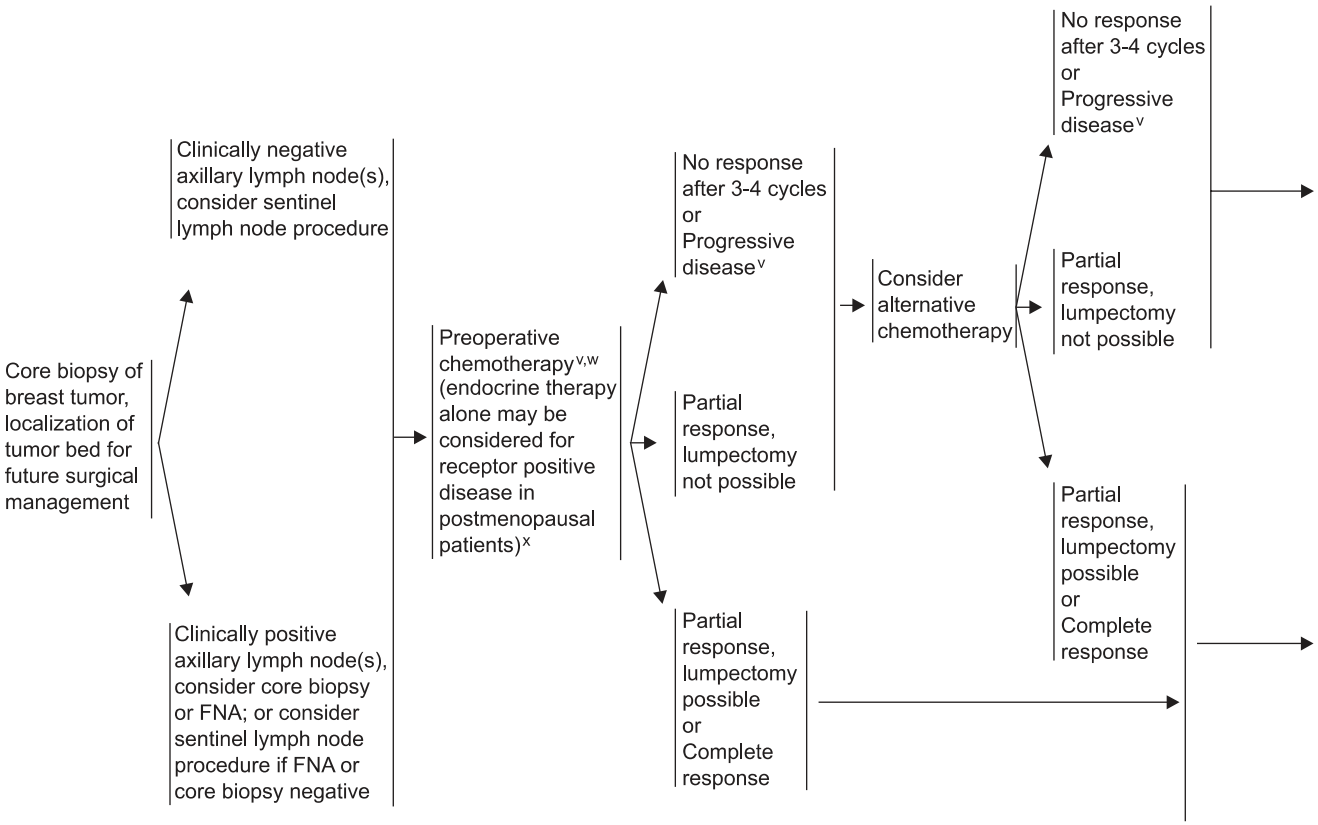
[t] Data are insufficient to make chemotherapy recommendations for patients > 70 y. Treatment should be individualized with consideration of comorbid conditions.

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 141).
[c] See Principles of Dedicated Breast MRI Testing (page 142).
[d] The use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer.

PREOPERATIVE CHEMOTHERAPY GUIDELINE
PRIMARY TREATMENT



[d] See Surgical Axillary Staging (page 142).
[v] Several combination and single-agent chemotherapy regimens have activity in the preoperative setting. In general, those chemotherapy regimens recommended in the adjuvant setting (see pages 147-150) may be considered in the preoperative setting. If treated with endocrine therapy, an aromatase inhibitor is preferred for postmenopausal women.
[w] Patients with HER2-positive tumors should be treated with preoperative chemotherapy incorporating trastuzumab for at least 9 weeks of preoperative therapy (see pages 147-150).
[x] Definition of Menopause (see page 151).

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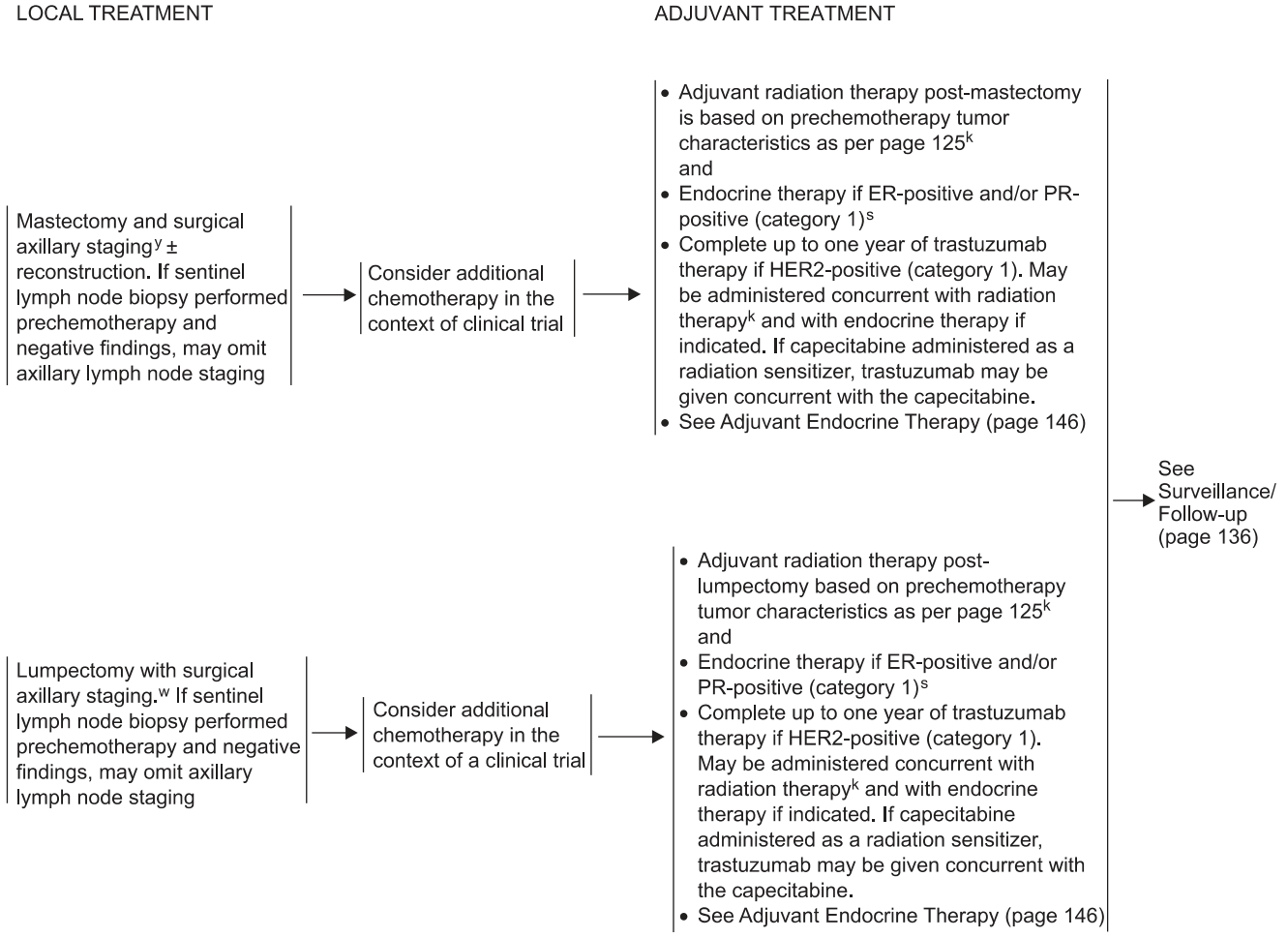
PREOPERATIVE CHEMOTHERAPY GUIDELINES



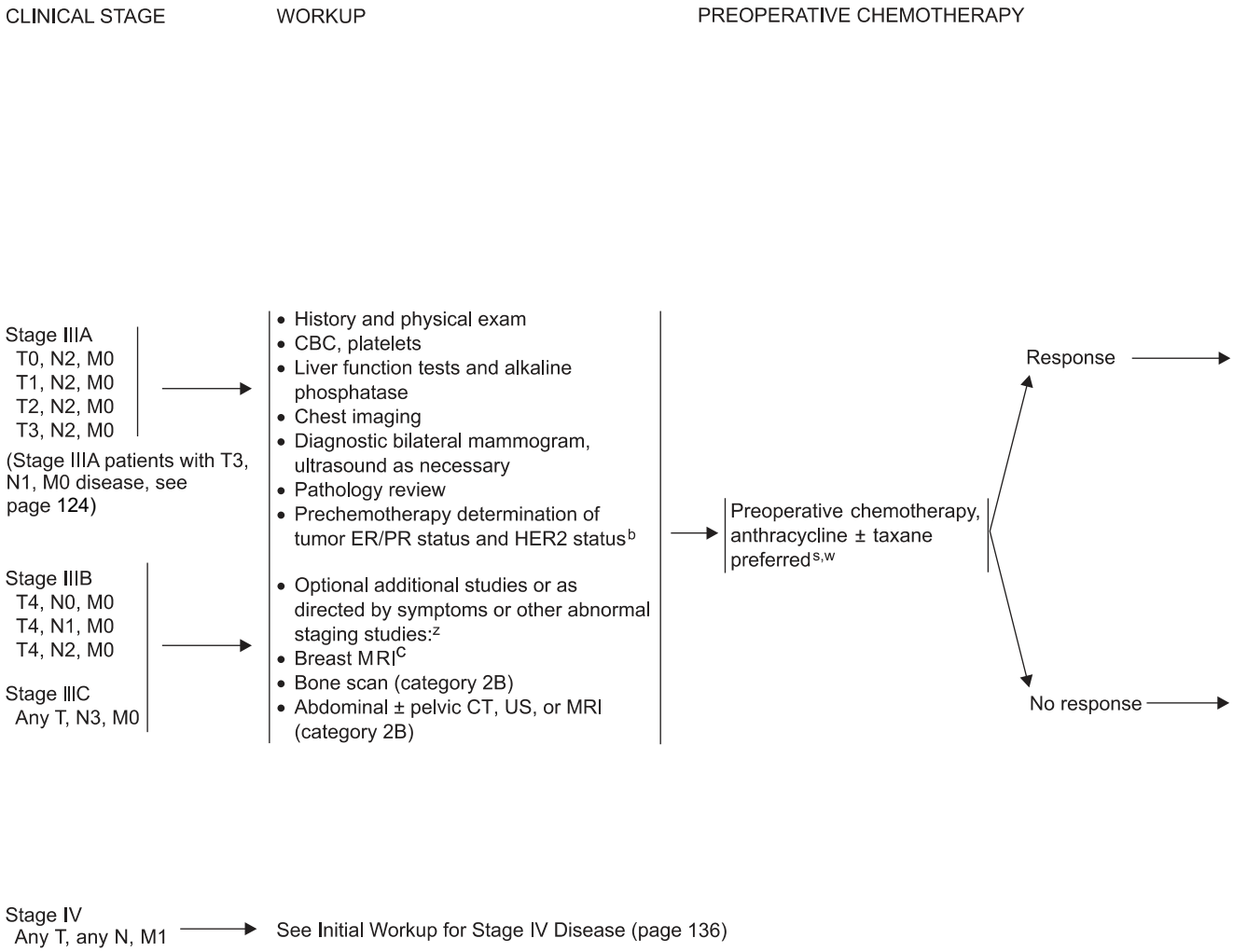
[k] See Principles of Radiation Therapy (page 145).

[s] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following 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 and in women aged ≥ 60 y where the incremental benefit of chemotherapy may be smaller. Available data suggest sequential or concurrent endocrine therapy with radiation therapy is acceptable.

[w] Patients with HER2-positive tumors should be treated with preoperative chemotherapy incorporating trastuzumab for at least 9 weeks of preoperative therapy (see pages 147-150).

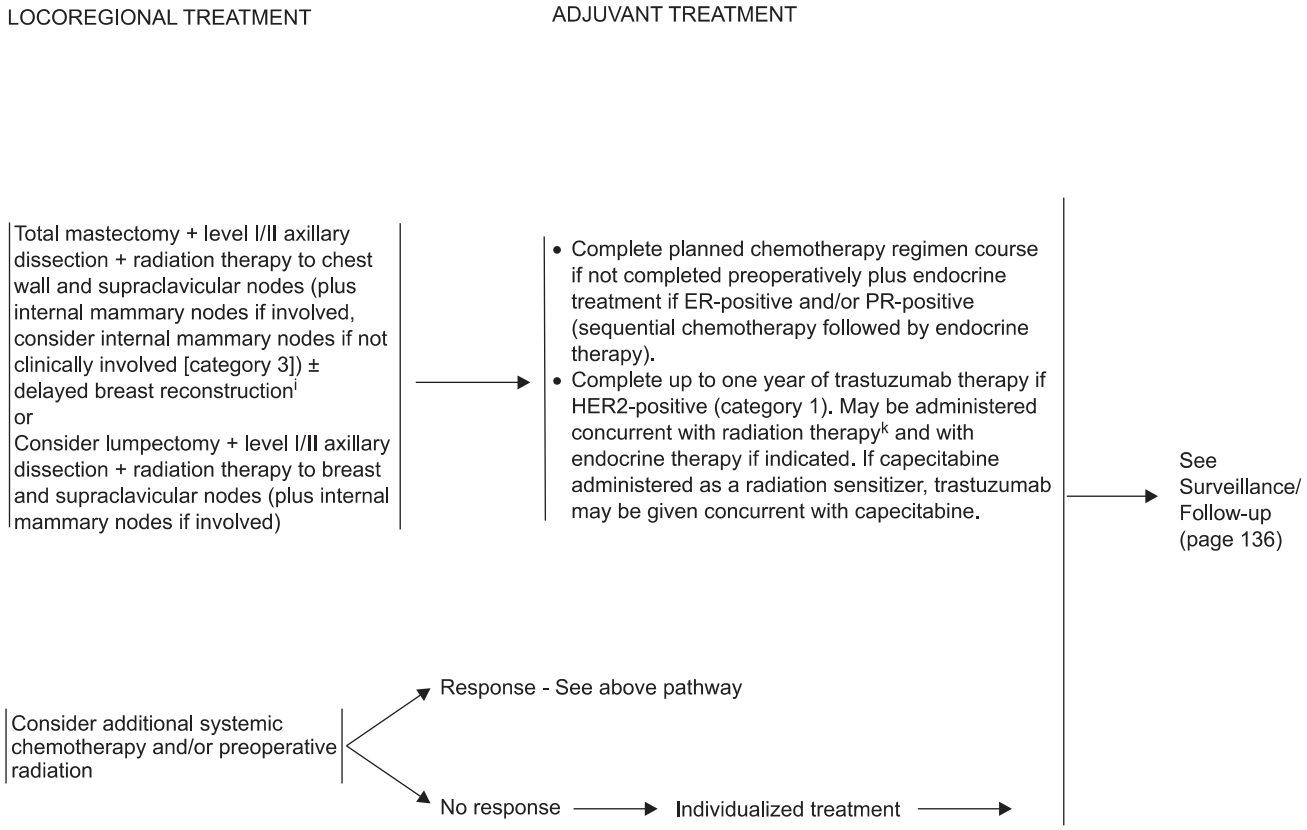
[y] Axillary staging may include sentinel node biopsy (category 3) or level I/II dissection.

LOCALLY ADVANCED INVASIVE BREAST CANCER (NONINFLAMMATORY)



Stage IV
Any T, any N, M1 → See Initial Workup for Stage IV Disease (page 136)

[b] See Principles of HER2 Testing (page 141).
[c] See Principles of Dedicated Breast MRI Testing (page 142).
[s] Several combination and single-agent chemotherapy regimens have activity in the preoperative setting. In general, those chemotherapy regimens recommended in the adjuvant setting (see pages 147-150) may be considered in the preoperative setting. If treated with endocrine therapy, an aromatase inhibitor is preferred for postmenopausal women.
[w] Patients with HER2-positive tumors should be treated with preoperative chemotherapy incorporating trastuzumab for at least 9 weeks of preoperative therapy (see pages 147-150).
[z] The use of PET or PET/CT scanning should generally be discouraged for the evaluation of locally advanced disease except in those clinical situations in which other staging studies are equivocal or suspicious. Even in these situations, biopsy of equivocal or suspicious sites is more likely to provide useful information.



[i] See Principles of Breast Reconstruction Following Surgery (page 144).
[k] See Principles of Radiation Therapy (page 145).
[s] Several combination and single-agent chemotherapy regimens have activity in the preoperative setting. In general, those chemotherapy regimens recommended in the adjuvant setting (see pages 147-150) may be considered in the preoperative setting. If treated with endocrine therapy, an aromatase inhibitor is preferred for postmenopausal women.
[w] Patients with HER2-positive tumors should be treated with preoperative chemotherapy incorporating trastuzumab for at least 9 weeks of preoperative therapy (see pages 147-150).

SURVEILLANCE/FOLLOW-UP

- Interval history and physical exam every 4-6 mo for 5 y, then every 12 mo
- Mammogram every 12 mo (and 6-12 mo post-radiation therapy if breast conserved [category 2B])
- Women on tamoxifen: annual gynecologic assessment every 12 mo if uterus present
- Women on an aromatase inhibitor or who experience ovarian failure secondary to treatment should have monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter[aa]
- Assess and encourage adherence to adjuvant endocrine therapy

→

RECURRENCE WORKUP
or
INITIAL WORKUP FOR STAGE IV DISEASE

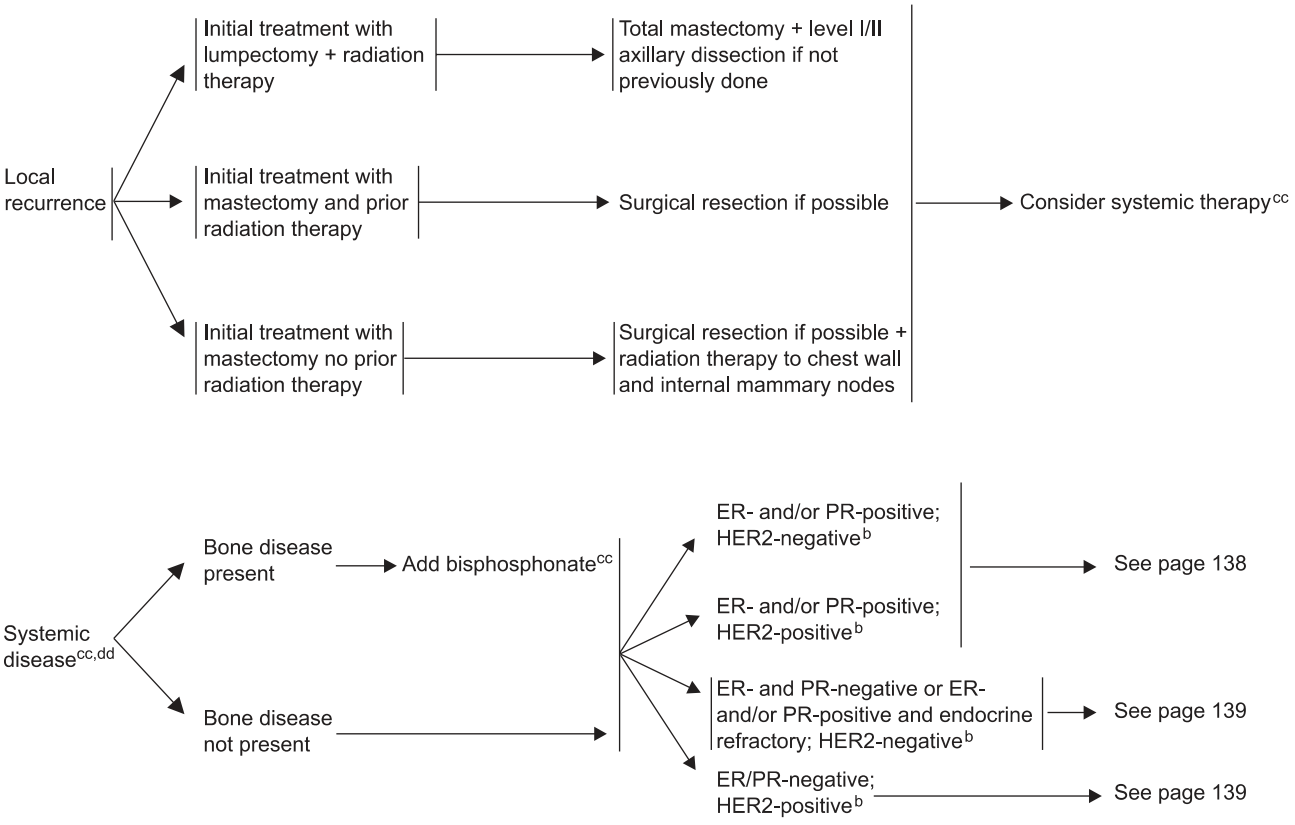
- History and physical exam
- CBC, platelets
- Liver function tests
- Chest imaging
- Bone scan
- X-rays of symptomatic bones and long and weight-bearing bones abnormal on bone scan
- Consider abdominal CT or MRI[bb]
- Biopsy documentation of first recurrence, if possible
- Consider determination of tumor ER/PR and HER2 status if unknown, originally negative or not overexpressed[b]

[b] See Principles of HER2 Testing (page 141).

[aa] The use of estrogen, progesterone, or selective ER 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. Current clinical trials support the use of a bisphosphonate for up to 2 years. Longer duration of bisphosphonate therapy may provide additional benefit but this has not yet been tested in clinical trials. Women treated with a bisphosphonate should undergo a dental examination with preventive dentistry prior to the initiation of therapy, and should take supplemental calcium (1200-1500 mg/d) and vitamin D (400-800 IU/d).

[bb] The use of PET or PET/CT scanning generally should be discouraged for the evaluation of metastatic disease except in those clinical situations in which 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 OF STAGE IV DISEASE



Surgery, radiation ± hyperthermia (category 3 for hyperthermia), 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

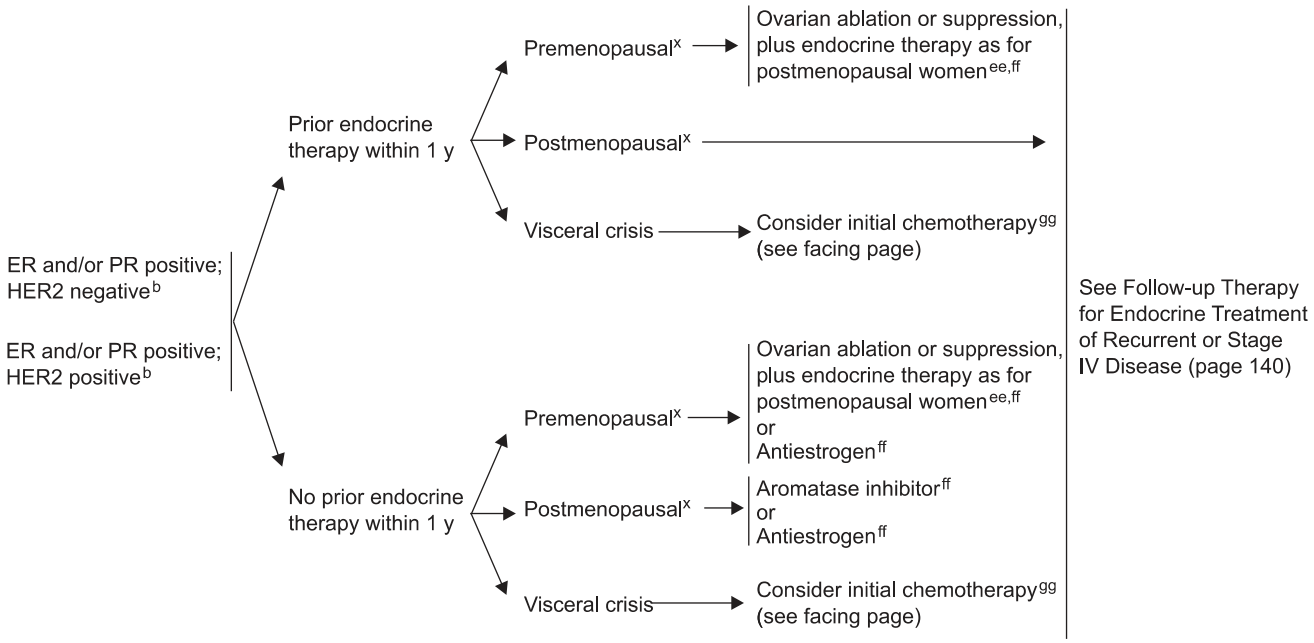
[b] See Principles of HER2 Testing (page 141).

[cc] Pamidronate or zoledronic acid (with calcium, 1200-1500 mg, and vitamin D, 400-800 IU, daily supplement) should be given (category 1) in addition to chemotherapy or endocrine therapy if bone metastasis present, expected survival ≥ 3 mo, and creatinine < 3.0 mg/dL. Patients should undergo a dental examination with preventive dentistry before initiation of bisphosphonate therapy.

[dd] See the NCCN Clinical Practice Guidelines in Oncology: Palliative Care. For the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org.

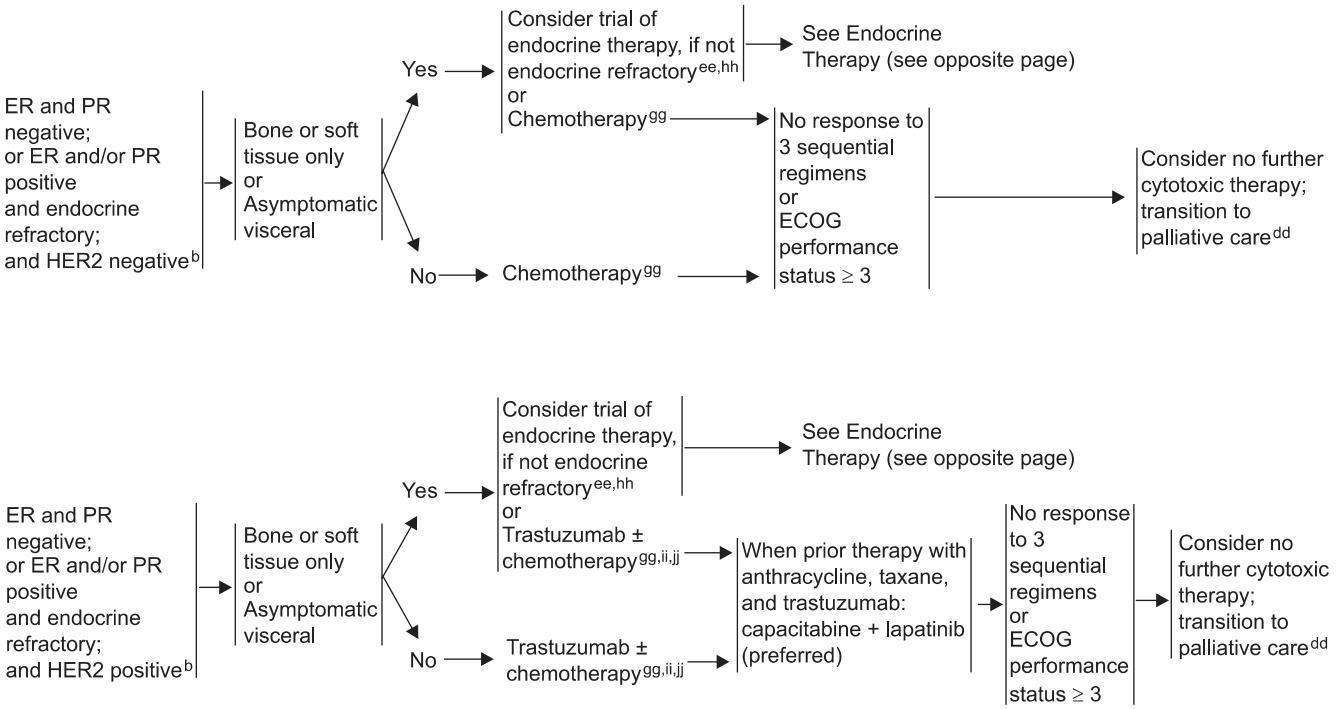
SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE

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



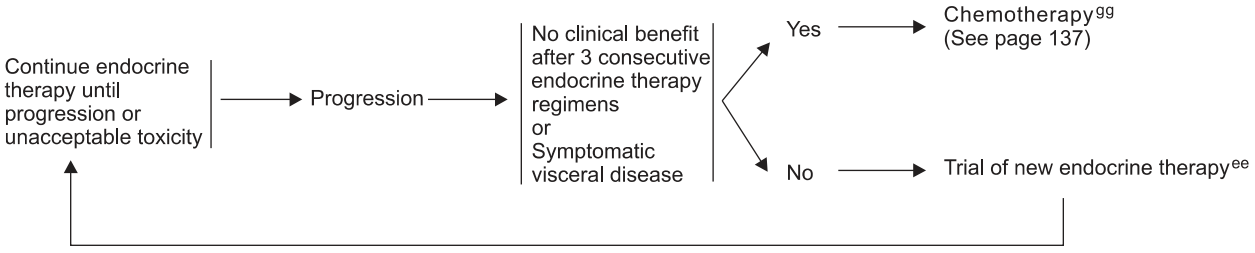
[b] See Principles of HER2 Testing (page 141).
[x] Definition of Menopause (page 151).
[ee] See Subsequent Endocrine Therapy for Systemic Disease (page 151).
[ff] Women presenting with metastatic disease at initial diagnosis may benefit from the performance of local breast surgery and/or radiation therapy. Generally this palliative local therapy should be considered only after response to initial systemic therapy.
[gg] See Preferred Regimens for Metastatic Disease (pages 152-155).

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



[b] See Principles of HER2 Testing (page 141).
[dd] See the NCCN Palliative Care Guidelines.
[ee] See Subsequent Endocrine Therapy for Systemic Diseae (page 151).
[gg] See Preferred Regimens for Metastatic Disease (pages 152-155).
[hh] 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 those with clinical characteristics predicting for a hormone receptor-positive tumor (e.g., long disease-free interval, limited sites of recurrence, indolent disease, older age).
[ii] The value of continued trastuzumab following progression on first-line trastuzumab containing chemotherapy for metastatic breast cancer is unknown. The optimal duration of trastuzumab in patients with long-term control of disease is unknown.
[jj] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity.

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



[ee] See Subsequent Endocrine Therapy (page 151).
[gg] See Preferred Regimens for Metastatic Disease (pages 152-155).

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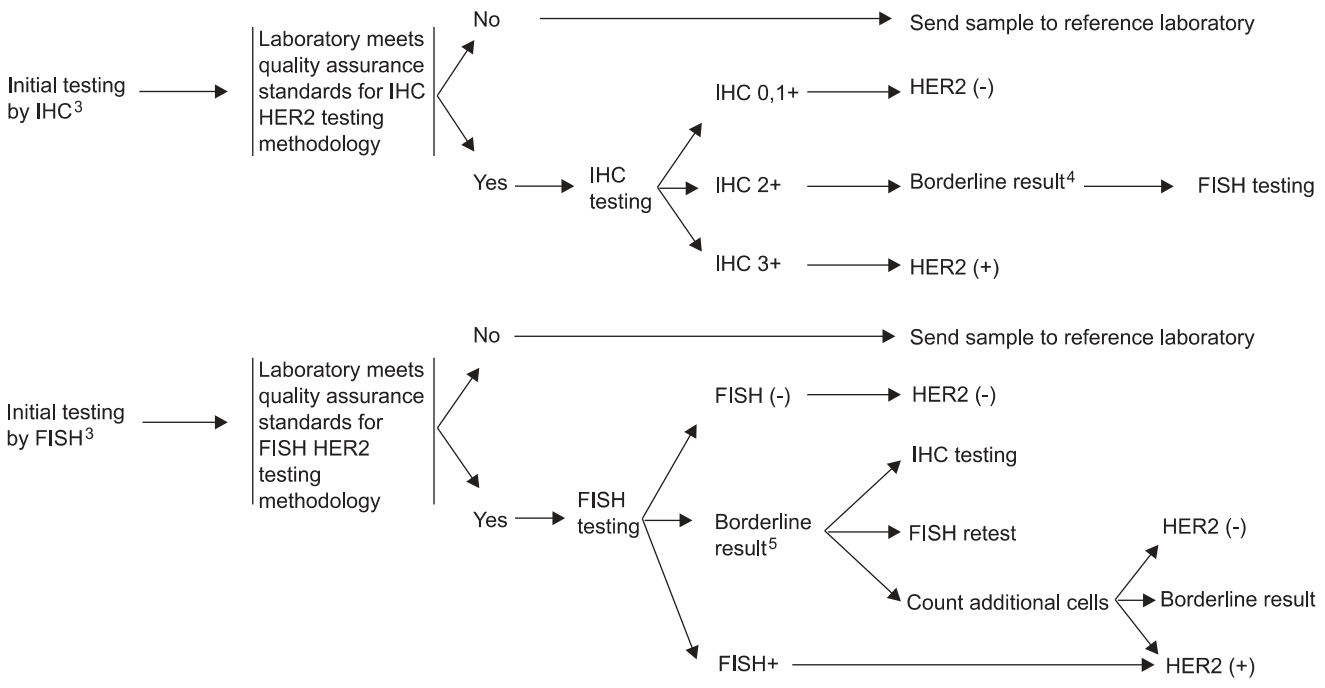
PRINCIPLES OF HER2 TESTING[1,2]



[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):S1-24.

[2] HER2 testing should be done only in laboratories accredited to perform such testing. Ongoing proficiency testing and full reporting of HER2 assay methods and results are required. A laboratory may perform only those tests which have been demonstrated 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 lab 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 nonamplified 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 to 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 which is at least 95% concordant with FISH as described above.

PRINCIPLES OF DEDICATED BREAST MRI TESTING

See NCCN Clinical Practice Guidelines in Oncology: 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:

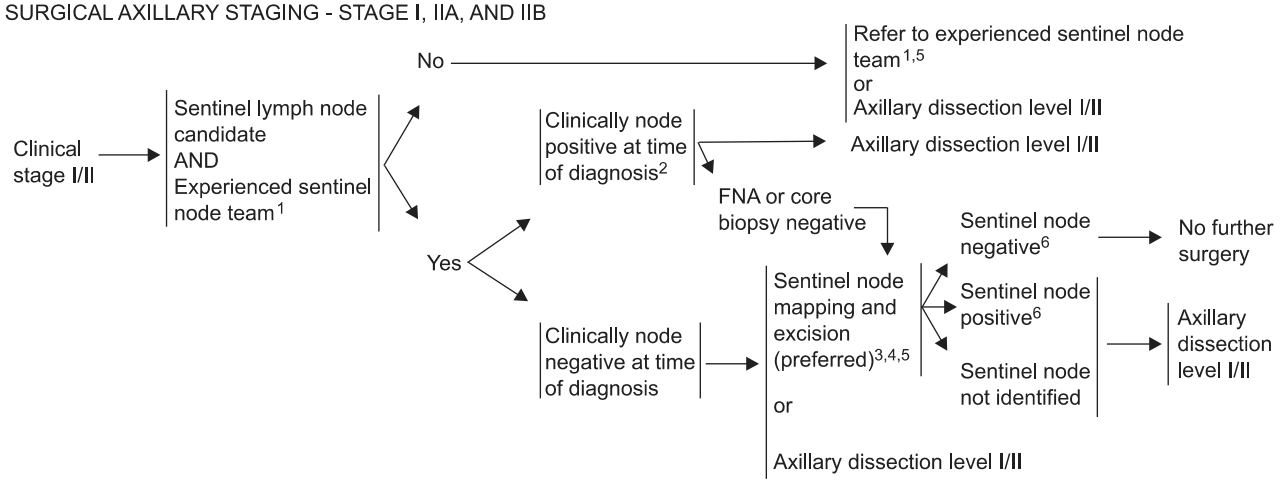
- Breast MRI examinations should be performed and interpreted by an expert breast imaging team working in conjunction with the multidisciplinary treatment team.
- Breast MRI examinations require a dedicated breast coil and breast imaging radiologists familiar with the optimal timing sequences and other 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 time of initial diagnosis (category 2B). No data show that use of MRI to affect choice of 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 for identifying primary cancer in women with axillary nodal adenocarcinoma or with 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.
- Utility in follow-up screening of ipsilateral and contralateral breast of women with prior breast cancer is not defined.

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.

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, 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 defined by multilevel node sectioning with hematoxylin and eosin staining. Cytokeratin IHC may be used for equivocal cases on H&E. Routine cytokeratin IHC to define node involvement is controversial (category 3).

AXILLARY LYMPH NODE STAGING

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

MARGIN STATUS IN INFILTRATING CARCINOMA

The use of breast conserving therapy is predicated on achieving a pathologically negative margin of resection. Cases that have 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 done with 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

[1]An extensive intraductal component is defined as an infiltrating ductal cancer where greater than 25% of the tumor volume is DCIS and DCIS extends beyond the invasive cancer into surrounding normal breast parenchyma.

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[1]

Relative:
- Active connective tissue disease involving the skin (especially scleroderma and lupus)
- Tumors > 5 cm (category 2B)
- Focally positive margin[1]
- Women ≤ 35 y or premenopausal women with a known BRCA 1/2 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 Clinical Practice Guidelines in Oncology: Breast Cancer Risk Reduction; to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org)

[1]See Margin Status in Infiltrating Carcinoma (page 143).

PRINCIPLES OF BREAST RECONSTRUCTION AFTER SURGERY

- The breast can be reconstructed in conjunction with mastectomy using breast implants, autologous tissue ("flaps"), or a combination of the two (e.g., latissimus/implant composite reconstructions).
- Breast reconstruction for mastectomy can be performed at the same time as mastectomy ("immediate") or at some time following the completion of cancer treatment ("delayed").
- As with any mastectomy, there is a risk for 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.
- 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 for 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 for 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 for complications in all types of breast reconstruction, whether with implant or flap. Smoking is therefore considered a relative contraindiction 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 delineation includes most the breast tissue, and is best performed through both clinical assessment and CT-based treatment planning. A uniform dose distribution is the objective, using compensators such as wedges, forward planning using segments, or intensity-modulated radiation therapy (IMRT). The breast should receive a dose of 45-50 Gy in 1.8 to 2 Gy/fraction, or 42.5 Gy at 2.66 Gy/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 10-16 Gy at 2 Gy/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 been reconstructed or not, several techniques using photons and/or electrons are appropriate. CT-based treatment planning is encouraged in order 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.

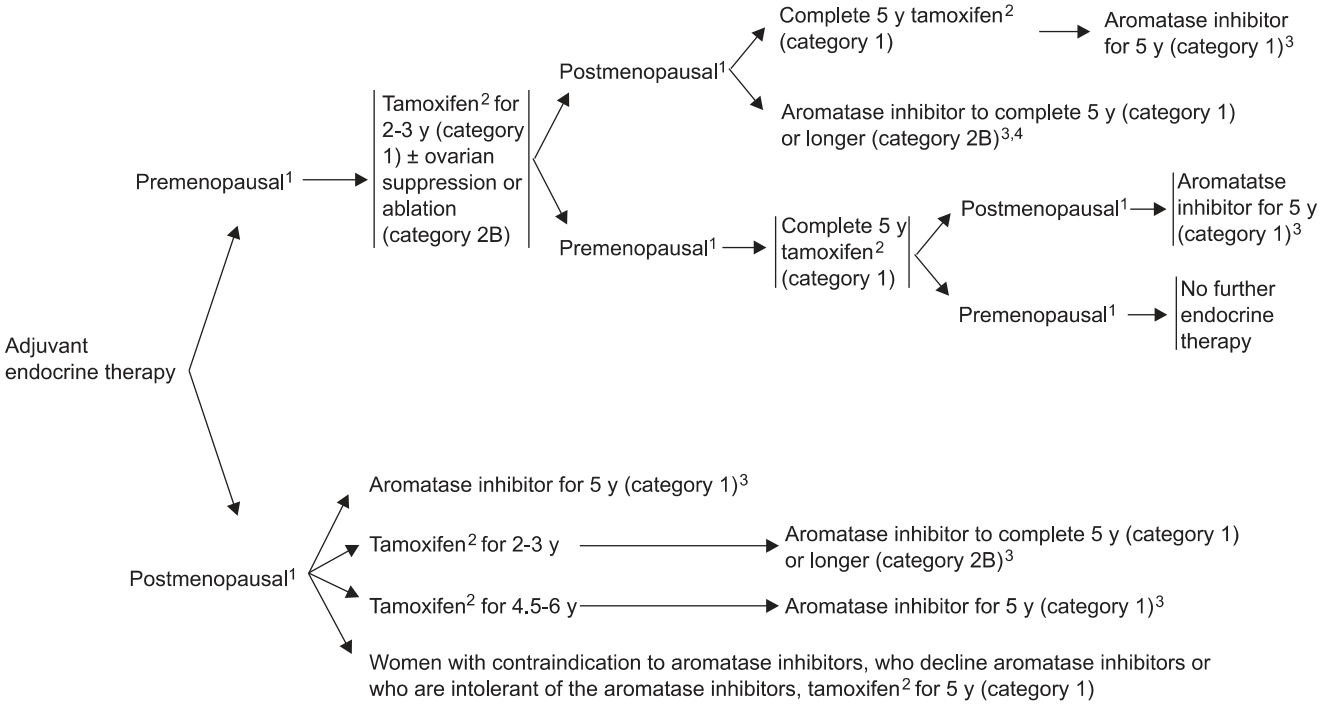
Regional Nodal Radiation:
Target delineation is best achieved by the use of CT-based treatment planning. For the paraclavicular and axillary nodes, prescription depth varies based on the size of the patient. For internal mammary node identification, the internal mammary artery and vein location can be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

Dose is 50 Gy, given as 1.8 to 2.0 Gy 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 treatment planning should be used in all cases where radiation therapy is delivered to the internal mammary lymph node field.

Partial Breast Irradiation (PBI):
PBI should be performed only as part of a prospective trial. PBI can be delivered with brachytherapy or external beam radiation using 3D conformal radiation or IMRT. If not trial eligible, PBI should be reserved for patients at low risk for recurrence. The target includes the tumor bed and a 1-cm margin. A 1 to 1.5 cm margin should be added when using photon radiation, to account for respiration. 34 Gy in 10 fractions delivered twice per day with brachytherapy or 38.5 Gy in 10 fractions delivered twice per day with photon radiation is prescribed the edge of the target. Intraoperative radiation with photons or electrons with a single fraction (targeted intraoperative radiotherapy) can be used in institutions with that expertise and experience.

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 151).
[2]Some serotonin reuptake inhibitors decrease the formation of endoxifen, an active metabolite of tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. The clinical impact of these observations is not known.
[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 resume ovarian function after discontinuation of tamoxifen and initiation of an aromatase inhibitor. Therefore, serial monitoring of plasma estradiol and FSH 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 151).

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

ADJUVANT CHEMOTHERAPY [1,2,3,4,5,6]

NON-TRASTUZUMAB-CONTAINING REGIMENS (all category 1)

Preferred Adjuvant Regimens:
- TAC (docetaxel/doxorubicin/cyclophosphamide)
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks
- AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel
- TC (docetaxel and 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 weeks
- AC followed by paclitaxel every 3 weeks
- EC (epirubicin/cyclophosphamide)
- A followed by T followed by C (doxorubicin followed by paclitaxel followed by cyclophosphamide) every 2 weekly regimen with filgrastim support
- FEC followed by T (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel)

TRASTUZUMAB-CONTAINING REGIMENS (all category 1)

Preferred Adjuvant Regimen:
- 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:
- 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 and because of 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 (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 year (with the exception of the docetaxel + trastuzumab followed by FEC regimen in which trastuzumab is given for 9 weeks), with cardiac monitoring, and by either the weekly or 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 following chemotherapy.
[5]For node-positive patients, anthracycline-containing chemotherapy regimens are preferred.
[6]Randomized clinical trials demonstrate that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.

NON-TRASTUZUMB-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[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)

AC followed by paclitaxel chemotherapy[3,4,5]
- 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 day 1 and 8
- 5-Fluorouracil 500 mg/m^2 IV days 1 and 8

Cycled every 28 days for 6 cycles

FEC 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

AC followed by paclitaxel chemotherapy[3,4,5]
- 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 175-225 mg/m^2 by 3-h IV infusion 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[2]
- 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

TRASTUZUMAB CONTAINING COMBINATIONS

PREFERRED ADJUVANT COMBINATIONS

AC followed by T chemotherapy with trastuzumab[15]
- 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 the 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 the completion of paclitaxel, and given to complete 1 y of trastuzumab treatment

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

*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 and 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: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.

AC followed by T chemotherapy with trastuzumab[15]
- 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[16]
- 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

OTHER ADJUVANT REGIMENS

Docetaxel + trastuzumab followed by FEC chemotherapy[17]
- 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[18]
- 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[17]
- 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[19]
- Trastuzumab 4 mg/kg IV for 1 dose beginning just prior to 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 on days 1 and 4
- Epirubicin 75 mg/m^2 IV on day 1
- Cyclophosphamide 500 mg/m^2 on day 1

Cycled every 21 days for 4 cycles

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 and 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.

REFERENCES FOR ADJUVANT CHEMOTHERAPY REGIMENS FOR BREAST CANCER

[1]Martin, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 2005;352:2302-1313.

[2]Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup trial C9741/Cancer and Leukemia Group B trial 9741. J Clin Oncol 2003;21:1431-1439.

[3]Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 2003;21:976-983.

[4]Mamounas EP, Bryant J, Lembersky BC, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP 13-28. J Clin Oncol 2005;23:3686-3696.

[5]Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in adjuvant treatment of breast cancer. N Engl J Med 2008;258:1663-1671.

[6]Jones S, Holmes F, O'Shaughnessey J, et al. Extended follow-up and analysis by age of the US Oncology Adjuvant Trial 9735: docetaxel/cyclophophamide is associated with an overall survival benefit compared to doxorubicin/cyclophosphamide and is well tolerated in women 65 or older. Presented at the San Antonio Breast Cancer Symposium; December 13-16, 2007; San Antonio, Texas. Abstract 12.

[7]Fisher B, Brown AM, Dimitrov NV, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with six months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from NSABP B-15. J Clin Oncol 1990;8:1483-1496.

[8]Buzdar AU, Kau SW, Smith TL, Hortobagyi GN. Ten-year results of FAC adjuvant chemotherapy trial in breast cancer. Am J Clin Oncol 1989;12;123-128.

[9]Assikis V, Buzdar A, Yang Y, et al. A phase III trial of sequential adjuvant chemotherapy for operable breast carcinoma: final analysis with 10-year follow-up. Cancer 2003;97:2716-2723.

[10]Bull JM, Tormey DC, Li SH, et al. A randomized comparative trial of adriamycin versus methotrexate in combination drug therapy. Cancer 1978;41:1649-1657.

[11]Levine MN, Bramwell VH, Pritchard KI, et al. Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1998;16:2651-2658.

[12]Goldhirsch A, Colleoni M, Coates AS, et al. Adding adjuvant CMF chemotherapy to either radiotherapy or tamoxifen: are all CMFs alike? The International Breast Cancer Study Group (IBCSG). Ann Oncol 1998;9:489-493.

[13]Piccart MJ, Di Leo A, Beauduin M, et al. Phase III trial comparing two dose levels of epirubicin combined with cyclophosphamide with cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. J Clin Oncol 2001;19:3103-3110.

[14]Roche H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 001 trial. J Clin Oncol 2006;24:5664-5671.

[15]Romond EH, Perez EZ, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2 positive breast cancer. N Engl J Med 2005;353:1673-1684.

[16]Robert NJ, Eiermann W, Pienkowski T, et al. BCIRG 006: docetaxel and trastuzumab-based regimens improve DFS and OS over AC followed by T in node positive and high risk node negative HER2 positive early breast cancer patients: quality of life at 36 mo [abstract]. J Clin Oncol 2007;25(Suppl 1):Abstract 19647.

[17]Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006;354:809-820.

[18]Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER-2 positive breast cancer. N Engl J Med 2005;353:1659-1672.

[19]Buzdar A, Ibrahim N, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 2005;23:3676-3685.

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DEFINITION OF MENOPAUSE

Clinical trials in breast cancer have used a variety of definitions of menopause. Menopause is generally the permanent cessation of menses, and as the term is 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 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and 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 as a component of endocrine therapy.

SUBSEQUENT HORMONAL THERAPY FOR SYSTEMIC DISEASE
(For first-line hormonal therapy, see page 137)

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

POSTMENOPAUSAL PATIENTS

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

REGIMENS FOR METASTATIC DISEASE[1]

PREFERRED SINGLE AGENTS

Anthracyclines
- Doxorubicin
- Epirubicin
- Pegylated liposomal doxorubicin

Taxanes
- Paclitaxel
- Docetaxel
- Albumin-bound paclitaxel

Antimetabolites
- Capecitabine
- Gemcitabine

Other microtubule inhibitors
- Vinorelbine

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

PREFERRED AGENTS WITH BEVACIZUMAB
- Paclitaxel[2]

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]There is no compelling evidence that combination regimens are superior to sequential single agents.
[2]A single randomized clinical trial documents superior time to progression and survival with the combination of bevacizumab plus paclitaxel compared with paclitaxel alone for first-line chemotherapy of metastatic disease.

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

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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]

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

PREFERRED FIRST LINE AGENTS WITH TRASTUZUMAB FOR HER2 POSITIVE DISEASE

COMBINATIONS
PCH chemotherapy[26]
- Carboplatin AUC of 6 IV day 1
- Paclitaxel 175 mg/m^2 IV day 1
Cycled every 21 days

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

SINGLE AGENTS
- Paclitaxel 175 mg/m^2 IV day 1[28]
Cycled every 21 days
OR
- Paclitaxel 80-90 mg/m^2 IV weekly[29]

- Docetaxel 80 to 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^2 PO twice daily days 1-14 [33]
Cycled every 21 days

TRASTUZUMAB COMPONENT

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]

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 and 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 AGENTS FOR TRASTUZUMAB-EXPOSED HER2-POSITVE DISEASE

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 + other first-line agents

Trastuzumab + capecitabine[35]

Trastuzumab + lapatinib[36]
Lapatinib 1000 mg PO daily

TRASTUZUMAB COMPONENT

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]

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 and 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.

REFERENCES FOR METASTATIC DISEASE

[1]Bull JM, Tormey DC, Li SH, et al. A randomized comparative trial of adriamycin versus methotrexate in combination drug therapy. Cancer 1978;41:1649-1657.

[2]Hortobagyi GN, Gutterman JU, Blumenschein GR, et al. Combination chemoimmunotherapy of metastatic breast cancer with 5-fluorouracil, adriamycin, cyclophosphamide, and BCG. Cancer 1979;43:1225-1233.

[3]Ackland SP, Anton A, Breitbach GP, et al. Dose-intensive epirubicin-based chemotherapy is superior to an intensive intravenous cyclophosphamide, methotrexate, and fluorouracil regimen in metastatic breast cancer: a randomized multinational study. J Clin Oncol 2001;19:943-953.

[4]Fisher B, Brown AM, Dimitrov NV, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with six months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from NSABP B-15. J Clin Oncol 1990;8:1483-1496.

[5]Langley RE, Carmichel J, Jones AL, et al. Phase III trial of epirubicin plus paclitaxel compared with epirubicin plus cyclphosphamide as first-line chemotherapy for metastatic breast cancer: United Kingdom Cancer Research Institute. J Clin Oncol 2005;23:8322-8330.

[6]Gianni L, Munzone E, Capri G, et al. Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. J Clin Oncol 1995;13:2688-2699.

[7]Nabholtz J-M, Falkson C, Campos D, et al. Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. J Clin Oncol 2003;21:968-975.

[8]Bonadonna G, Brusamolino E, Valagussa P, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 1976;294:405-410.

[9]O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 2002;20:2812-2823.

[10]Albain KS, Nag S, Calderillo-Ruiz G, et al. Global phase III study of gemcitabine plus paclitaxel (GT) vs. paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): first report of overall survival [abstract]. J Clin Oncol 2004;22(Suppl 1):Abstract 510.

[11]Chan S, Friedrichs K, Noel D, et al. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. J Clin Oncol 1999;17:2341-2454.

[12]Gundersen S, Kvinnsland S, Klepp O, et al. Weekly adriamycin versus VAC in advanced breast cancer. A randomized trial. Eur J Cancer Clin Oncol 1986;22:1431-1434.

[13]Bastholt L, Dalmark M, Gjedde SB, et al. Dose-response relationship of epirubicin in the treatment of postmenopausal patients with metastatic breast cancer: a randomized study of epirubicin at four different dose levels performed by the Danish Breast Cancer Cooperative Group. J Clin Oncol 1996;14:1146-1155.

[14]O'Brien ME, Wigler N, Inbar M, et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HC1 (CAELYX/Doxil) vs. conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol 2004;15:440-449.

[15]Seidman A, Tiersten A, Hudis C, et al. Phase II trial of paclitaxel by 3-hour infusion as initial and salvage chemotherapy for metastatic breast cancer. J Clin Oncol 1995;13:2575-2581.

[16]Perez EA, Vogel CL, Irwin DH, et al. Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. J Clin Oncol 2001;19:4216-4223.

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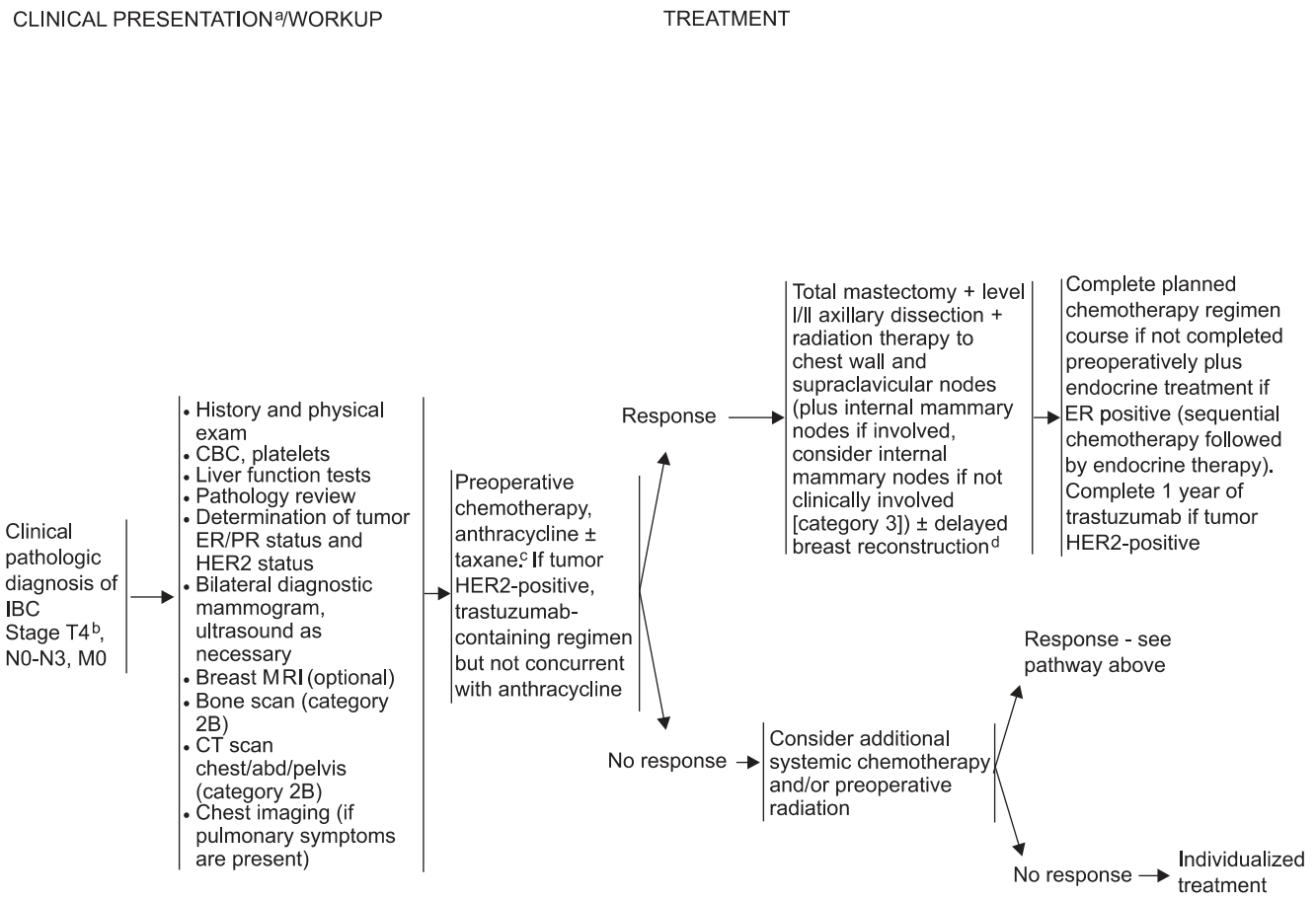
[17]Burris HAR. Single-agent docetaxel (Taxotere) in randomized phase III trials. Semin Oncol 1999;26:1-6.
[18]Valero V. Docetaxel as single-agent therapy in metastatic breast cancer: clinical efficacy. Semin Oncol 1997;24(Suppl 13):S11-18.
[19]Burstein HJ, Manola J, Younger J, et al. Docetaxel administered on a weekly basis for metastatic breast cancer. J Clin Oncol 2000;18:1212-1219.
[20]Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 2005;23:7794-7803.
[21]Gradishar W, Krasnojon D, Cheporov S, et al. Randomized comparison of weekly or every-3-week nab-paclitaxel compared to q3w docetaxel as first-line therapy in patients with metastatic breast cancer [abstract]. J Clin Oncol 2007;25(Suppl 1):Abstract 1032.
[22]Bajetta E, Procopio G, Celio L, et al. Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. J Clin Oncol 2005;23:2155-2161.
[23]Seidman AD. Gemcitabine as single-agent therapy in the management of advanced breast cancer. Oncology (Williston Park) 2001;15(Suppl 3):11-14.
[24]Zelek L, Barthier S, Riofrio M, et al. Weekly vinorelbine is an effective palliative regimen after failure with anthracyclines and taxanes in metastatic breast carcinoma. Cancer 2001;92:2267-2272.
[25]Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007;357:2666-2676.
[26]Robert N, Leyland-Jones B, Asmar L, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. J Clin Oncol 2006;24:2786-2792.
[27]Perez E. Carboplatin in combination therapy for metastatic breast cancer. Oncologist 2004;9:518-527.
[28]Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783-792.
[29]Seidman AD, Berry D, Cirrincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol 2008;26:1642-1649.
[30]Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol 2005;23:4265-4274.
[31]Esteva FJ, Valero V, Booser D, et al. Phase II study of weekly docetaxel and trastuzumab for patients with HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002;20:1800-1808.
[32]Burstein HJ, Keshaviah A, Baron AD, et al. Trastuzumab plus vinorelbine or taxane chemotherapy for HER2-overexpressing metastatic breast cancer: the trastuzumab and vinorelbine or taxane study. Cancer 2007;110:965-972.
[33]Bartch R, Wenzel C, Altorjai G, et al. Capecitabine and trastuzumab in heavily pretreated metastatic breast cancer. J Clin Oncol 2007;25:3853-3858.
[34]Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355:2733-2743.
[35]Von Minckwitz G, Zielinski C, Maarteense E, et al. Capecitabine vs capecitabine + trastuzumab in patients with HER2-positive metastatic breast cancer progressing during trastuzumab treatment: the TBP phase III study (GBG 26/BIG 3-05) [abstract]. J Clin Oncol 2008;26(Suppl 1):Abstract 1025.
[36]O'Shaughnessy J, Blackwell KL, Burstein H, et al. A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on trastuzumab therapy [abstract]. J Clin Oncol 2008;26(Suppl 1):Abstract 1015.
[37]Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999;17:2639-2648.
[38]Leyland-Jones, Gelmon, Ayoub JB, et al. Pharmacokinetics, safety, and efficacy of trastuzumab administered every three weeks in combination with paclitaxel. J Clin Oncol 2003;21:3965-3971.



[a] Inflammatory breast cancer is a clinical syndrome in women with invasive breast cancer that is characterized by erythema and edema (peau d'orange) of a third or more of the skin of the breast and with a palpable border to the erythema. The differential diagnosis includes cellulitis of the breast or mastitis. Pathologically, tumor is typically present in the dermal lymphatics of the involved skin, but dermal lymphatic involvement is neither required for, nor sufficient for by itself, a diagnosis of inflammatory breast cancer.

[b] Patients with stage IV or recurrent IBC should be treated according to the guideline for recurrence/stage IV disease (pages 136-140).

[c] Patients with HER2-positive tumors should be considered for chemotherapy incorporating trastuzumab (see pages 147-150).

[d] See Principles of Breast Reconstruction Following Surgery (page 144).

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Text continued from p. 123

reduction strategies (see NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Risk Reduction; to view the most recent version of these guidelines, visit www.nccn.org).

Proliferative abnormalities of the breast are limited to the lobular and ductal epithelium. In both, 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. The 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 of *JNCCN* are sections of the guidelines on noninvasive breast cancer and special considerations in breast cancer.

Pathology Assessment

A central component of breast cancer treatment is full knowledge of disease extent and biologic features. These factors help determine disease stage, help estimate the risk for cancer recurrence, and provide information that predicts response to therapy (e.g., hormone receptors and human epidermal growth factor receptor 2 [HER2]). These factors are determined by examining excised tissue and provided in a written pathology report. Accurate pathology reporting requires the clinician and pathologist to communicate about relevant patient history, prior breast biopsies, prior irradiation to the chest, pregnancy status, characteristics of the abnormality biopsied (e.g., palpable, mammographically detected, microcalcifications), clinical state of lymph nodes, presence of inflammatory change or other skin abnormality, and any prior treatment administered (e.g., chemotherapy, radiotherapy). The specimens should be oriented for the pathologist and specific requests stated to determine biomarkers (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.

The College of American Pathologists (CAP) has developed pathology reporting protocols to promote complete, 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 free on the CAP Web site at www.cap.org.

Consistent, unambiguous, and complete pathology reporting is a cornerstone of quality breast cancer care, and the NCCN Breast Cancer Panel endorses using the CAP protocols for reporting the pathologic analysis of all breast specimens.

Treatment Approach

Conceptually, the treatment of breast cancer includes the treatment of local disease with surgery, radiotherapy, 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. These factors include 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 they should be treated similarly to postmenopausal women, except that the use of aromatase inhibitors is ineffective without concomitant suppression of testicular steroidogenesis.[7,8] 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 can be divided into 1) the pure noninvasive carcinomas, including lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS; stage 0); 2) operable, local-regional 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 124). Genetic counseling is recommended if the patient is considered at high risk for hereditary breast cancer as defined by the NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Guidelines (available at www.nccn.org).

Using MRI to evaluate women considering breast-conserving therapy is optional. 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 142). The limitations of breast MRI include a high percentage of false-positive findings.[9–11] MRI 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).

No randomized, prospective assessment of the efficacy of MRI in the staging or treatment decision making in breast cancer treatment are available. One retrospective study suggested an outcome benefit,[12] whereas another did not.[13] One systematic review[11] documented that breast MRI staging altered surgical treatment in 7.8% to 33.3% of women.[11] However, no differences in outcome, if any, were 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.

Additional staging studies involving bone scan or abdominal imaging using CT, ultrasound, or MRI are optional. These studies are not indicated in patients with stage I disease without signs/symptoms of metastatic disease, nor are they needed in many other patients with early-stage breast cancer.[14] Radionuclide bone scanning and abdominal imaging with CT, ultrasound, or MRI are typically indicated only for patients with signs or symptoms related to bone or abdomen (e.g., bone scan if alkaline phosphatase is elevated, abdominal scan if liver function tests are abnormal) or those with T3N1M0 disease (category 2B for bone scan). These recommendations are supported by a study evaluating patients with newly diagnosed breast cancer using bone scan, liver ultrasonography, and chest radiography.[15] Bone scan identified metastases 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 those with stage I or II disease.

The panel recommends against using PET or PET/CT scanning to stage these patients. PET scanning is not recommended because of the high false-negative rate in detecting lesions that are small (< 1 cm) and/or low-grade, relatively low sensitivity for detecting axillary nodal metastases, low prior probability of the patients having detectable metastatic disease, and high rate of false-positive scans.[16–21]

Along with ER and PR status, the guidelines specify determining HER2 status for all newly diagnosed invasive breast cancers. HER2 status can be assessed through measuring the number of *HER2* gene copies (using fluorescence in situ hybridization [FISH]), or with a complementary method to assess the quantity of HER2 cell-surface receptors (e.g., immunohistochemistry [IHC]).[22] Five methods currently are FDA approved for determining the HER2 status of breast cancer tumors: 1) IHC HercepTest (DAKO, Glostrup, Denmark);[23] 2) IHC Pathway HER2 test (Ventana Medical Systems, Tucson, Arizona);[24] 3) INFORM HER2 FISH test (Ventana Medical Systems);[25] 4) PathVysion HER2 FISH test (Vysis, Downers Grove, Illinois);[26] and 5) SPOT-Light HER2 CISH test (Invitrogen, Carmarillo, California).[27] However, many anatomic pathology laboratories are currently using modifications 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[28–32] and false-negative[28,33] HER2 test results are common. An NCCN task force has reviewed this topic and issued recommendations on HER2 testing in breast cancer,[34] which are summarized in the guideline (see page 141). The panel considers either IHC or FISH acceptable for making an initial determination of HER2 tumor

status provided that the test method was validated and shown to be at least 95% concordant with another validated method. Evidence for 95% concordance between the HER2 assay used and a validated complementary HER2 testing method is also required. Breast cancer tumors are classified as HER2-positive if they demonstrate *HER2* gene amplification using a FISH method or are scored as 3+ with an IHC 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 IHC) are described in the guideline (see page 141).

HER2 testing should be performed only in laboratories accredited to perform this testing. Furthermore, these laboratories should have established standardized HER2 testing procedures and programs to periodically evaluate the proficiency of personnel performing the testing. Test reports must provide information on site of tumor; specimen type; histologic type; fixation method and time; block examined; testing method used; results of ongoing validation and concordance studies of the HER2 testing methods used in that laboratory; and other laboratory quality assurance information. Clinicians should be familiar with the significance of these criteria when making individual clinical recommendations.

A joint panel from ASCO and CAP has recently 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.[35] The panel endorses CAP accreditation for anatomic pathology laboratories performing HER2 testing.

Determining the HER2 status of the tumor is recommended for prognostic purposes for patients with node-negative breast cancer.[36] HER2 tumor status also provides baseline predictive information used in selecting optimal adjuvant/neoadjuvant therapy and in selecting therapy for recurrent or metastatic disease (category 1). For example, retrospective analyses have shown that anthracycline-based adjuvant therapy is superior to non–anthracycline-based adjuvant chemotherapy in patients with HER2-positive tumors,[37–41] and that the dose of doxorubicin may be important in treating HER2-positive tumors.[42] However, prospective evidence of the predictive efficacy of HER2 status in early-stage[43–46] and metastatic breast cancer[47–49] is currently available only for trastuzumab-containing therapies.

ER and PR tumor status is normally determined using IHC testing. Although this method is considered reliable when performed by experienced pathology personnel, there have been a number of reports indicating that the reliability of ER and PR determinations can vary widely from one laboratory to another.[50–52] These interlaboratory differences may be attributable to the diverse methodologies and diverse interpretation schema used to evaluate tumor hormonal status.

Locoregional Treatment

Several randomized trials document that mastectomy with axillary lymph node dissection is equivalent to breast-conserving therapy with lumpectomy, axillary dissection, and whole breast irradiation, as primary breast treatment for most women with stage I and II breast cancers (category 1).[53–56] When breast-conserving therapy with lumpectomy and radiation therapy is performed, the panel considers the data inadequate to support the use of partial breast irradiation outside the confines of a high-quality, prospective clinical trial.[57] The panel recommends whole breast irradiation to include most of the breast tissue. Breast irradiation should be performed after CT-based treatment planning to limit exposure of the heart and lungs to radiation, 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) are recommended.[58] 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 were found to provide comparable disease-free and overall survival in a study of women with node-negative early-stage breast cancer with a median follow-up of 69 months.[59] Randomized trials have shown decreased in-breast recurrences with an additional boost dose of radiation (through photons, brachytherapy, or electron beam) to the tumor bed.[60,61] The relative reduction in risk for local recurrence with the addition of a boost is similar across age groups (from ≤ 40 to > 60 years), whereas the absolute gain in local control is highest in younger patients. A benefit has been shown favoring a boost in patients with positive axillary nodes, lymphovascular invasion, or close margins (see page 145). For example, a subset analysis from an

EORTC trial, including only patients (1724 patients of 5318 total) for whom central pathology review of tumor margins was available, 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.[62] Hence, the panel recommends considering administering a boost after postlumpectomy whole breast irradiation (see page 125).

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 with local excision through a single incision with a satisfactory cosmetic result; or have positive pathologic margins (see pages 143 and 144). Patients with a pathologically positive margin should generally undergo re-excision to achieve a negative pathologic margin. If the margins remain positive after re-excision, then mastectomy is 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 greater than 5 cm (category 2B), and focally positive pathologic margins (see page 144). Those patients with focally positive pathologic margins who do not undergo re-excision 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 increased likelihood of ipsilateral breast tumor recurrence after breast-conserving surgery or mastectomy.[63–65] Risk factors, such as a family history of breast cancer or a genetic predisposition for breast cancer (e.g., *BRCA1/2* or other mutation), are more likely to exist in the population of young women with breast cancer, thereby confounding the independent contributions of age and treatment to clinical outcome.[66] Survival outcomes are similar for young women with breast cancer undergoing either breast-conserving therapy or mastectomy.[67] The panel recommends that women with breast cancer who are 35 years or younger or premenopausal and carriers of a known *BRCA1/2* mutation consider additional risk-reduction strategies (see page 144 and the NCCN Breast Cancer Risk Reduction and Genetic/Familial High-Risk Assessment: Breast and Ovarian Guidelines).

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% for patients in the lumpectomy, radiation, and tamoxifen arm, and 4% for those in the lumpectomy plus tamoxifen arm. No differences were seen in overall or disease-free survival, or need for mastectomy.[68] An updated analysis of this study with a median follow-up of 8.2 years confirmed these results.[69] Similar results were obtained in another study of similar design.[70] The 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 breast cancer (category 1 with tamoxifen; category 2A with an aromatase inhibitor).

If adjuvant chemotherapy is indicated after breast-conserving surgery, radiation should typically be given after chemotherapy is completed.[71] Breast-conserving radiotherapy may be given concurrent with CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy, but methotrexate should either be withheld during the radiation or limited to no more than 2 doses concurrent with the radiation. Concurrent CMF chemotherapy with radiation has been shown to decrease the cosmetic outcome of breast-conserving therapy in some studies.[72–74] The guideline includes a recommendation for regional lymph node irradiation in patients treated with breast-conserving surgery (see page 125) in situations analogous to those recommended for patients treated with postmastectomy regional lymph node irradiation (see pages 125 and 145 and subsequent discussion).

These guidelines include a treatment guideline for surgical staging of the axilla for stages I, IIA, and IIB breast cancer (see page 142). 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 axilla as the preferred method to assess the pathologic status of the axillary lymph nodes for patients with stage I or II breast cancer[75–83] (see page 142). This recommendation is supported by results of recent randomized clinical trials showing decreased arm and shoulder morbidity (e.g., pain, lymphedema, and sensory loss) in patients with breast cancer undergoing sentinel lymph node biopsy compared with those undergoing standard axillary node dissection.[82,84] No significant differences were seen between in these studies in the effectiveness of the sentinel lymph node procedure or level I and II dissection in 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.[85,86] Referral to an experienced sentinel lymph node team for the definitive surgical treatment of the breast and surgical axillary lymph node staging should be considered for women who have clinical stage I or II disease and do not have immediate access to an experienced sentinel node team. 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 H&E staining and cytokeratin IHC 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 IHC is unclear. Because the historical and clinical trial data on which treatment decisions are based rely on H&E staining, the panel believes that current treatment decisions should be made based solely on H&E staining (category 3). In the uncommon situation in which H&E staining is equivocal, relying on the results of cytokeratin IHC is reasonable.

Level I or II axillary dissection is an appropriate staging study in women with invasive breast cancer. Although the option of sentinel lymph node mapping and excision is preferred by the panel over axillary lymph node dissection as the initial axillary lymph node staging for women with clinically node-negative stage I or II breast cancer, it is not a mandatory replacement for a level I and II axillary dissection. Axillary lymph node dissection 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 should be provided for pathologic evaluation to accurately stage the axilla.[87,88] 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 axillary lymph node dissection or sentinel lymph node resection, these procedures may be considered optional in patients who have particularly favorable tumors, in those for whom the selection of adjuvant systemic therapy is unlikely to be affected by the results of the procedure, elderly patients, and those with serious comorbid conditions (see page 143). Women who do not undergo axillary dissection or axillary lymph node irradiation are at increased risk for ipsilateral lymph node recurrence.[89] Those 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 those 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 considering either a core biopsy or FNA of these nodes, along with a sentinel node biopsy if biopsy results are negative.[90] Preoperative chemotherapy is not indicated unless invasive breast cancer is confirmed. Recommended staging studies are outlined on page 131 and include history and physical examination, CBC, platelet count, liver function tests, diagnostic bilateral mammogram (with ultrasound as necessary), pathology review, and determination of tumor ER/PR and HER2 status. Breast MRI, bone scan, and abdominal imaging are optional unless the patient is symptomatic or as directed based on other abnormal or suspicious staging evaluations; chest imaging is recommended if pulmonary symptoms are present.

The current guideline lists prechemotherapy sentinel lymph node resection as the preferred option for surgical axillary staging in women with clinically negative ipsilateral axillary examinations (see page 142). If the sentinel lymph node is histologically negative, omission of the axillary dissection may be considered at local surgical therapy. If the sentinel lymph node is histologically positive, then level I and II axillary dissection should be performed at 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 sentinel lymph node is positive) should be performed at definitive surgical therapy.

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 preoperative chemotherapy is administered, both the prechemotherapy clinical and postchemotherapy pathologic nodal stages must be used to determine the risk for 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 sufficient tumor response that breast-conserving therapy becomes possible. Because complete or near-complete clinical responses are common, the use of percutaneously placed clips into the breast under mammographic or ultrasound guidance or other method of localizing prechemotherapy tumor volume aids in the postchemotherapy resection of the original area of tumor and is encouraged. Results of the NSABP (National Surgical Adjuvant Breast and Bowel Project) B-18 trial show that breast conservation rates are higher after preoperative chemotherapy.[91] 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 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 involving 2411 women documented a higher rate of complete pathologic response at local therapy in patients treated preoperatively with 4 cycles of AC followed by 4 cycles of docetaxel versus 4 cycles of preoperative AC. Disease-free and overall survival have not been shown to be superior after docetaxel treatment in B-27.[92] A disease-free survival advantage was observed (hazard ratio [HR], 0.71; 95% CI, 0.55–0.91; $P = .007$) favoring preoperative over 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 147–150) are appropriate to consider in the preoperative chemotherapy setting. In women with HER2-positive tumors treated with neoadjuvant chemotherapy, the addition of neoadjuvant trastuzumab to paclitaxel followed by FEC chemotherapy was associated with an increase in the pathologic complete response rate from 26% to 65.2% ($P = .016$).[93] Thus, incorporating trastuzumab into neoadjuvant chemotherapy regimens seems important in treating HER2-positive tumors.

Several randomized trials have assessed the value of neoadjuvant endocrine therapy in treating

postmenopausal women with ER-positive breast cancer. These studies have generally compared the rates of objective response and rates of breast-conserving surgery among treatment with tamoxifen, anastrozole, anastrozole plus tamoxifen, or letrozole. These studies consistently show that using either anastrozole or letrozole alone provides superior rates of breast-conserving surgery and usually objective response.[94,95] Based on these trials, preoperative endocrine therapy with an aromatase inhibitor is an option in treating postmenopausal women with hormone receptor–positive disease.

If the tumor responds to preoperative chemotherapy, lumpectomy plus (if prechemotherapy sentinel lymph node staging was not performed 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 132 and 133). If a prechemotherapy sentinel lymph node procedure was performed and it 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. The panel agrees that no role exists for postoperative chemotherapy if a full course of standard chemotherapy has been 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 in women with ER- and/or PR-positive tumors. Up to 1 year of trastuzumab therapy should be completed if the tumor is HER2-positive (category 1). Radiation should be delivered to the chest wall and supraclavicular lymph nodes (see page 145). Inclusion of the internal mammary lymph nodes in the radiotherapy field can be considered, but this recommendation generated substantial controversy among panel members (category 3). Postmastectomy radiotherapy in patients with T2N0M0 tumors may be considered optional.

Capecitabine can be administered as a radiation sensitizer for patients at high risk for local recurrence (category 2B). Endocrine therapy and trastuzumab can be administered concurrent with radiation therapy if indicated. If capecitabine is administered as a radiation sensitizer, trastuzumab may be given concurrently.

Radiation Therapy After Mastectomy

***Node-Positive Disease*:** Three randomized clinical trials have shown that a disease-free and overall survival advantage is 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.[96–100] In these trials, the ipsilateral chest wall and ipsilateral locoregional lymph nodes were irradiated. These studies contrast, however, with several other studies, including a randomized trial from an NCCN institution that failed to show a survival advantage with postmastectomy chest wall and regional node irradiation.[101] However, based on the studies showing a survival advantage with postmastectomy chest wall and regional lymph node irradiation in node-positive breast cancer, the current guidelines call for postmastectomy irradiation in women with 4 or more positive axillary lymph nodes, and strong consideration of postmastectomy irradiation in women with 1 to 3 positive axillary lymph nodes.

Two retrospective analyses have provided some evidence for benefit of radiotherapy for only selected patients undergoing preoperative chemotherapy before mastectomy.[102,103] However, the panel recommends that decisions related to administration of radiation therapy for patients undergoing neoadjuvant chemotherapy should be made on the basis of prechemotherapy tumor characteristics, irrespective of tumor response to preoperative chemotherapy (i.e., radiotherapy is recommended in patients with clinical stage III disease and a pathologic complete response to neoadjuvant chemotherapy). For women with 1 to 3 involved axillary lymph nodes, the panel recommends strongly considering radiation to the chest wall and supraclavicular area after chemotherapy (category 1), with consideration also given to the inclusion of the ipsilateral internal mammary nodal field (category 3).

The recommendation for chest wall and supraclavicular irradiation in women with 1 to 3 involved axillary lymph nodes 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.[104] 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. However, other members believe radiation should be considered in this setting but should not be mandatory based on the studies that do not show an advantage. This is an unusual situation in which high-level evidence (category 1) exists but is contradictory.[54,97,98,100,104] Women with 1 to 3 involved axillary lymph nodes and tumors greater than 5 cm or with positive pathologic margins postmastectomy should undergo postchemotherapy radiation therapy to the chest wall and supraclavicular areas (category 1), with consideration given to including the ipsilateral internal mammary field (category 3).

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 it was in the studies that showed an advantage for postmastectomy, postchemotherapy radiotherapy. Therefore, this recommendation is identified as category 3.

Women with 4 or more positive axillary lymph nodes are at substantially increased risk for locoregional recurrence of disease. Postmastectomy postchemotherapy chest wall and regional lymph node irradiation is recommended (category 1). The use of prophylactic chest wall irradiation in this setting substantially reduces the risk for local recurrence.[54] Again, substantial disagreement existed among panel members regarding the inclusion of the ipsilateral internal mammary field (category 3).

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. An 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.[105] Consideration should be given to radiation of the ipsilateral supraclavicular area (category 2B) and the ipsilateral internal mammary lymph nodes (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 radiotherapy 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: Several factors must be considered when deciding on breast reconstruction after mastectomy (see page 144). First, several different types of breast reconstruction are available, including reconstruction using implants, autologous tissue, or both. Implant reconstruction typically involves the placement of a sub–pectoralis major expander implant, a series of expansions, followed by replacement of the expander with a permanent sub–pectoralis major implant. Several different techniques are available for the performance of autologous reconstruction using various combinations of muscle, fat, and skin from various donor sites. The type of reconstruction chosen depends on patient preference, body habitus, smoking history, comorbidities, plans for irradiation, and expertise and experience of the reconstruction team. For many patients, reconstruction may be performed as an immediate procedure while under the same anesthetic as the mastectomy. 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.

When breast reconstruction after mastectomy is planned, close prospective evaluation and collaboration between members of the breast cancer treatment team is essential, including both the oncologic and reconstructive surgeons and the other members of the multidisciplinary team.

***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.[106] 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, thereby avoiding 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.[107,108]

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, while better preserving the natural shape and appearance of the breast than do standard breast resections.[109] 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, the 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 age groups younger than 70 years undergoing polychemotherapy and in all age groups receiving tamoxifen.[2] Thus, for patients younger than 70 years, the current guidelines recommend adjuvant therapy without regard to patient age (category 1). When considering 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 taken into account and balanced.[110,111] The decision-making process requires a collaboration involving the health care team and the patient.

Estimating Risk For 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,[110] and a validated computer-based model (i.e., Adjuvant! Online at www.adjuvantonline.com) is available to estimate 10-year disease-free and overall survival that incorporates all of the above prognostic factors except for HER2 tumor status.[111,112] These tools help clinicians to objectively estimate outcome with local treatment only and the absolute benefits expected from systemic adjuvant endocrine therapy and chemotherapy. These estimates may be used by the clinician and patient when considering the toxicities, costs, and benefits of systemic adjuvant therapy.[113]

Use of DNA microarray technologies to characterize breast cancer has allowed the development of classification systems of breast cancer according to gene expression profile.[114] Five major subtypes of breast cancer have been identified by DNA microarray gene expression profiling: ER-positive/HER2-negative (luminal A and luminal B subtypes); ER-negative/HER2-negative (basal subtype); HER2-positive; and tumors with characteristics similar to normal breast tissue (normal breast–like).[115–117] 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.[118] 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.[119–121]

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 (Oncotype Dx). On retrospective analysis of 2 trials (NSABP B-14 and B-20) performed in women with hormone receptor–positive, axillary lymph node–negative invasive breast cancer, this assay system was able to quantify risk for recurrence as a continuous variable (e.g., Oncotype Dx recurrence score) and to predict responsiveness to both tamoxifen and CMF or methotrexate/5-fluorouracil/leucovorin chemotherapy.[122,123] A recent comparison of simultaneous analyses of breast cancer tumors using 5 different gene-expression models indicated that 4 of these methods (including MammaPrint and Oncotype Dx) provided similar predictions of clinical outcome.[124]

Although many DNA microarray technologies are able to stratify patients into prognostic and/or predictive subsets on retrospective analysis, the gene subsets differ from study to study, and prospective clinical trials testing the usefulness of these techniques have yet to be reported. Currently, 2 prospective randomized clinical trials (TAILORx and MINDACT) are addressing the use of Oncotype 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 0.6 to 1.0 cm with unfavorable features or larger than 1 cm, and node-negative, hormone receptor–positive, and HER2-negative (category 2B). In this circumstance, the recurrence score may be determined to assist in estimating likelihood of recurrence and benefit from chemotherapy (category 2B). The panel emphasizes that the recurrence score should be used for decision-making only in the context of other elements of risk stratification for individual patients. All recommendations involving use of the recurrence score in treatment decision-making are categorized as 2B (see page 128).

Axillary Lymph Node–Negative Tumors: The prognosis for 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 as treatment of the invasive breast cancer. Tamoxifen may be considered to reduce the risk for a second contralateral breast cancer, especially in patients with ER-positive disease. The NSABP database showed a correlation between the ER status of a new contralateral breast tumor and the original primary tumor, reinforcing that tamoxifen is unlikely to be an effective strategy for reducing the risk for contralateral breast cancer in patients diagnosed with ER-negative tumors.[125] 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 for 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 decision to use endocrine therapy and chemotherapy in these relatively lower-risk subsets of women must balance the expected absolute risk reduction with the patient's willingness to experience toxicity to achieve that incremental risk reduction.

Patients with lymph node involvement or with tumors greater than 1 cm in diameter are appropriate candidates for adjuvant systemic therapy (category 1). For women with lymph node-negative, hormone receptor-negative tumors larger than 1 cm in diameter, chemotherapy is recommended (category 1). For those with lymph node-negative, hormone receptor-positive breast cancer tumors greater than 1 cm, endocrine therapy with chemotherapy is recommended (category 1). The incremental benefit of combination chemotherapy in patients with lymph node–negative, hormone receptor–positive breast cancer may be relatively small.[126] Therefore, the panel recommends that tumor hormone receptor status be included as a factor to consider when making chemotherapy-related treatment decisions for patients with node-negative, hormone receptor–positive breast cancer. This evaluation may be especially important for patients with tumors characterized as 0.6 to 1.0 cm and hormone receptor–positive with unfavorable features, or larger than 1 cm and hormone receptor–positive and

HER2-negative (see pages 127 and 128). However, chemotherapy should not be withheld from these patients solely based on ER-positive tumor status.[2,126,127]

The use of genomic/gene expression array data, which also incorporate additional prognostic/predictive biomarkers (e.g., Oncotype 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, evolution of chemotherapy and hormone therapy regimens, and overall more favorable prognosis of patients with lymph node–negative disease compared with those enrolled in the historically controlled clinical trials. Some NCCN institutions consider performing RT-PCR analysis (e.g., Oncotype DX assay) to further refine risk stratification of 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. In premenopausal women, adjuvant tamoxifen is preferred. If both chemotherapy and tamoxifen are used, 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.[127] Consequently, chemotherapy followed by endocrine therapy should be the preferred therapy sequence.

The paucity of clinical trial data regarding adjuvant chemotherapy in women older than 70 years prohibits definitive recommendations in this age group. Adjuvant treatment in women older 70 year should be individualized, with consideration of comorbid conditions.

***Guideline Stratification for Systemic Adjuvant Therapy*:** The current version of the guidelines first recognizes subsets of patients with early breast cancer of the usual histologies based upon responsiveness to endocrine therapy and trastuzumab (i.e., hormone receptor status, HER2 status; see page 126). Patients are then further stratified based on risk for recurrence of disease based on anatomic and pathologic characteristics (i.e., tumor grade, tumor size, axillary lymph node status, angiolymphatic invasion; see pages 127–129).

***Adjuvant Endocrine Therapy*:** These guidelines call for the determination of ER and PR content in all primary invasive breast cancers. 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 will be administered.[128] 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.[39,129–136] 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.[137] However, given the favorable toxicity profile of the available endocrine therapies, the panel recommends the use of adjuvant endocrine therapy in most women with hormone receptor–positive breast cancer regardless of menopausal status, age, or HER2 status of the tumor. The 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 where the prognosis is so favorable that the benefits of adjuvant endocrine therapy are very small.

The most firmly established adjuvant endocrine therapy for both premenopausal and postmenopausal women is tamoxifen.[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.[127]

Several studies have evaluated aromatase inhibitors in the treatment of postmenopausal women with early-stage breast cancer. These studies have utilized the aromatase inhibitors as initial adjuvant therapy, as sequential therapy following 2 to 3 years of tamoxifen, or as extended therapy following 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 page 151). The results from 2 prospective, randomized clinical trials have provided evidence of an overall survival benefit for patients with early-stage breast cancer receiving 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.[138,139] In addition, the Clinical Trials Group of the National Cancer Institute of Canada (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.[140] However, no survival differences have been reported for patients undergoing initial adjuvant therapy with an aromatase inhibitor versus first-line tamoxifen.[141,142] 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 for 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.[143,144] With a median of 100 months follow-up, results in 5216 postmenopausal women with hormone receptor–positive, early breast cancer enrolled in the ATAC trial demonstrated fewer recurrences (HR for disease-free survival, 0.85; 95% CI, 0.76–0.94; *P* = .003) with anastrozole compared with tamoxifen.[141] 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.[144] ATAC trial subprotocols show a lesser effect of anastrozole compared with tamoxifen on endometrial tissue,[145] similar effects of anastrozole and tamoxifen on quality of life, with most patients reporting no significant impairment of overall quality of life;[146] a greater loss of bone mineral density with anastrozole;[147] a small pharmacokinetic interference of anastrozole in the presence of tamoxifen of unclear significance;[148] and no evidence of an interaction between prior chemotherapy and anastrozole.[149]

BIG (Breast International Group) 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 versus letrozole alone, including those patients in the sequential arms during their first 2 years of treatment only.[142] 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, as was no difference in overall survival. A comparison of the cardiovascular side effects in the tamoxifen and letrozole arms of this trial showed a similar overall incidence of cardiac adverse events (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 were significantly higher in the tamoxifen arm.[150]

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.[151] The HR for relapse strongly favored sequential treatment with anastrozole (HR, 0.35; 95% CI, 0.18–0.68; *P* = .001) with a trend toward fewer deaths (*P* = .10).[151] 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.[152]

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.[153] The results at a median of 55.7 months of follow-up showed sequential exemestane to be superior in 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 ABCSG (Austrian Breast and Colorectal Cancer Study Group) 8 trial and the ARNO (Arimidex Nolvadex) 95 trial was also reported.[154] Patients in this combined analysis were randomized after 2 years of tamoxifen to complete 5 years of adjuvant tamoxifen or 3 years of anastrozole. With 28 months median follow-up available, 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, 0.0.53; 95% CI, 0.28–0.99; $P = .045$).[139] A meta-analysis of ABCSG 8, ARNO 95, and ITA showed significant improvement in overall survival (HR 0.71, 95% CI, 0.520–0.98; $P = .04$) with a switch to anastrozole.[155]

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 breast cancer.[140,156] 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 occurred (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; $P = .04$). In a separate cohort analysis of the MA-17 trial, the efficacy of letrozole versus placebo was evaluated after study unblinding in the 1579 woman who had been randomly assigned to placebo after 4.5 to 6 years of tamoxifen.[157] The median time since completion of tamoxifen was 2.8 years. Both disease-free survival 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 received 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.[158,159]

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 therapy, sequential therapy, or extended therapy. Thus, the current version of the guideline recommends that postmenopausal women with early 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 finds no compelling evidence that anastrozole, letrozole, and exemestane have meaningful differences in efficacy or toxicity. In postmenopausal women, the use of tamoxifen alone for 5 years is limited to those who decline or who have a contraindication to aromatase inhibitors (see page 147).

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 these women are to be considered for therapy with an aromatase inhibitor[160,161] (see page 151).

***Adjuvant Cytotoxic Chemotherapy*:** Several combination chemotherapy regimens are appropriate to consider when adjuvant cytotoxic chemotherapy is utilized (see pages 147–150). All adjuvant chemotherapy regimens listed in the guidelines have been evaluated in phase III clinical trials, and the current version of the adjuvant chemotherapy guideline does not distinguish options for chemotherapy regimens by 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 include fluorouracil, doxorubicin, and cyclophosphamide (FAC/CAF) or cyclophosphamide, epirubicin, and fluorouracil (FEC/CEF); epirubicin and cyclophosphamide (EC); cyclophosphamide, methotrexate, and fluorouracil (CMF); AC with sequential docetaxel administered every 3 weeks; AC with sequential paclitaxel 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); and FEC followed by docetaxel. The adjuvant chemotherapy guideline also includes specific representative doses and schedules for the recommended adjuvant chemotherapy regimens (see pages 147–150). Recent studies document substantial improvement in outcome with the incorporation of trastuzumab in the adjuvant treatment of HER2-positive breast cancer (see section on Adjuvant Trastuzumab Therapy).

New to the 2009 version of the guidelines is the preferred versus other designation for adjuvant chemotherapy regimens. The purpose of this distinction is to convey the panel's view of the relative efficacy and toxicity of the regimens.[162] 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 trial results focusing on treatment efficacy are summarized in the following discussions.

Studies of CMF chemotherapy versus no chemotherapy have shown disease-free and overall survival advantages with CMF chemotherapy.[2,163] Studies using FAC/CAF chemotherapy have shown that the use of full-dose chemotherapy regimens is important.[164] 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.[163] 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 treating HER2-positive breast cancers.[36,38,40,132,165,166] 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 such patients (see pages 147–150).

AC chemotherapy for 4 cycles has been studied in randomized trials, resulting in relapse-free and overall survival equivalent to CMF chemotherapy.[167–169] No benefit from dose escalation of either doxorubicin or cyclophosphamide was shown.[170,171] 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 1 showed an improvement in overall survival with the addition of paclitaxel.[171,172] On retrospective analysis, the apparent advantage of the paclitaxel-containing regimen seems greater in women with ER-negative breast cancers.

One randomized trial evaluated the use of concurrent versus sequential chemotherapy (doxorubicin followed by paclitaxel followed by cyclophosphamide vs. 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 regimens, but show a 26% reduction in hazard of recurrence (P = .01) and 31% reduction in the hazard of death (P = .013) for the dose-dense regimens.[173]

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 of the trial.[174] The second trial compared CEF given 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.[175] Another trial compared 2 dose levels of EC chemotherapy with CMF chemotherapy in women with node-positive breast cancer.[176] 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. An additional 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.[177] Five-year disease-free survival (78.4% vs. 73.2%; adjusted P = .012) and overall survival (90.7% vs. 86.7%; P = .017) were superior with sequential FEC followed by docetaxel.

Final results from a randomized trial comparing docetaxel, doxorubicin, and cyclophosphamide (TAC) versus FAC chemotherapy in axillary lymph node-positive breast cancer showed that TAC is superior to FAC.[178] Estimated 5-year disease-free survival with TAC was 75% and FAC 68% (HR, 0.72; 95% CI, 0.59–0.88; P = .001) and survival 87% with TAC and 81% with FAC (HR, 0.70; 95% CI, 0.53–0.91; P = .008). Disease-free survival favored TAC in both ER-positive and ER-negative tumors.

The ECOG E1199 study was a 4-arm trial that randomized 4950 women to undergo AC chemotherapy followed by either paclitaxel or docetaxel given by either an every-3-weekly schedule or a weekly schedule.[179,180] 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 with every-3-weekly administration. In a secondary series of comparisons, weekly paclitaxel was superior to every-3-weekly paclitaxel 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.[179]

At a median follow-up of 6.9 years, a trial randomizing 1016 women with stage I through III breast cancer to combination TC or AC chemotherapy[181] showed that overall disease-free (85% vs. 79%; P = .018) and overall survival (88% vs. 84%; P = .045) were significantly improved with TC compared with AC.

Several retrospective studies have evaluated the potential interaction of chemotherapy benefit and ER status.[2,126] These studies assessed the effect of chemotherapy on the risk for breast cancer recurrence in patients with ER-positive tumors undergoing adjuvant endocrine therapy when compared with patients 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.[126] showed that 22.8% more patients with ER-negative tumors survived without disease for 5 years if they underwent chemotherapy, whereas this benefit was only 7% for those with ER-positive tumors. The guideline therefore includes 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 moderately/poorly differentiated or with unfavorable features (see page 128).

Adjuvant Trastuzumab Therapy: Trastuzumab is a humanized, monoclonal antibody with specificity for the extracellular domain of HER2/neu; HER2.[182] Results of 5 randomized trials testing trastuzumab as adjuvant therapy have been reported.[43–46] 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 paclitaxel 4 cycles 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 the 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 the paclitaxel.[43] The joint analysis included 3968 patients and was performed at 4 years median follow-up. A 52% reduction in the risk for recurrence (HR, 0.48; 95% CI, 0.41–0.57; $P < .0001$) and a 35% reduction in the risk for death (HR, 0.65; 95% CI, 0.51–0.84; log-rank $P = .0007$) were documented.[183] Similar significant effects on disease-free survival were observed when results of these trials were analyzed separately. Patients treated with trastuzumab showed increased cardiac toxicity.[43,184,185]

In the adjuvant trastuzumab trials, the rates of grade III/IV congestive heart failure or cardiac-related death for patients receiving treatment regimens containing trastuzumab ranged from 0% (FinHer trial) to 4.1% (NSABP B-31 trial) overall.[43–46,184,185] 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 arms of the trial without trastuzumab, with trastuzumab after chemotherapy, and with trastuzumab initially combined with paclitaxel, respectively.[185] The acceptable rate of significant cardiac toxicity observed in the trastuzumab adjuvant trials partially 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.[186,187]

A third trial (Herceptin Adjuvant [HERA] Trial; N = 5081) tested trastuzumab for 1 or 2 years compared to 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.[44] At 1-year median follow-up, 1 year of trastuzumab resulted in a 46% reduction in the risk for recurrence compared with no trastuzumab (HR, 0.54; 95% CI, 0.43–0.67; $P < .0001$), no difference in overall survival, and acceptable cardiac toxicity. The 2-year data indicate that 1 year of trastuzumab therapy is associated with an overall survival benefit when compared with observation (HR for risk for death, 0.66; 95% CI, 0.47–0.91; $P = .0115$).[188]

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.[45] 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; $P < .0001$) when compared with the patients in 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.[46] Patients with HER2-positive cancers that were either node-positive or node-negative with tumors 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 for 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.

All of the adjuvant trials of trastuzumab show clinically significant improvements in disease-free survival, and the combined analysis from the NSABP B-31, NCCTG N9831, and HERA trials 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 guideline (category 1; see pages 147–150). The benefits of trastuzumab are independent of ER status.[43] Based on these studies, the panel 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 the preferred trastuzumab-containing adjuvant regimen, because this regimen has shown efficacy in 2 randomized clinical trials and has been associated with significant improvements in overall survival. The TCH regimen is also classified as a preferred regimen, especially in those with risk factors for cardiac toxicity, given the results of BCIG 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 141).

The panel has also recommended considering adjuvant trastuzumab in women with node-negative tumors that are 0.6 to 1.0 cm (see pages 127 and 129). Some support for this recommendation is provided by results of a retrospective study of 1245 women with early-stage breast cancer tumors characterized as T1pN0.[189] Among women with tumors characterized as HER2-positive, ER-positive, 10-year breast cancer–specific survival and 10-year recurrence-free survival were 85% and 75%, respectively, and 70% and 61%, respectively, in women with HER2-positive, ER-negative tumors. In addition, subgroup analyses from several of the randomized trials have shown consistent benefit of trastuzumab irrespective of tumor size or nodal status.[183,190] However, the recommendation to consider trastuzumab in patients with HER2-positive, ER-negative tumors that are 0.6 to 1.0 cm is designated as category 3 because patients with tumors smaller than 1 cm were not included in the available randomized trials, their risk overall for recurrence is relatively low, and the risk for cardiac toxicity diminishes the overall benefit.

***Adjuvant Therapy of Favorable Histology Tumors*:** These 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 130). 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 questioned if a tubular breast cancer is found to be ER-negative and/or HER2-positive. If a breast cancer is histologically identified as a tubular or colloid (mucinous) breast cancer and confirmed to be 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 had a lower potential for metastases and better prognosis than typical infiltrating ductal carcinoma. However, the best available evidence suggests that the risk for metastases equals that of other high-grade carcinomas, even for cases that meet all 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 of 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 that this classification is 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 have 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 patients with stage III invasive breast cancer is similar to that for patients with stage I or II disease (see page 134). The workup includes history and physical examination, CBC, 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. 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 2B), are optional unless directed by symptoms or other abnormal study results. The panel recommends that PET or PET/CT scans generally be discouraged for evaluating stage III disease, except when other staging studies are equivocal or suspicious (category 2B). Although very limited evidence shows the efficacy of PET scanning in staging patients with locally advanced disease,[18,21] the panel considers biopsy of equivocal or suspicious sites more likely than PET scanning to provide useful staging information for these patients. Genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer as defined by the NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Guidelines (to view the most recent version, visit the NCCN Web site at www.nccn.org).

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 guidelines and to determine 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 versus those who have clinical TanyN2M0 disease, based on evaluation by a multidisciplinary team. For patients with operable locally advanced disease, generally those with clinical T3N1M0 disease, treatment is as outlined on pages 124 through 128. 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 134. 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.[191] Patients with locally advanced HER2-positive breast cancer should undergo an initial chemotherapy program that incorporates preoperative trastuzumab (pages 147–150). Local therapy after a clinical response to preoperative chemotherapy usually consists of 1) total mastectomy with level I/II axillary lymph node dissection, with or without delayed breast reconstruction, or 2) lumpectomy and level I/II axillary dissection. Both local treatment groups are considered to have sufficient risk for 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 135).

Adjuvant therapy may involve completion of planned chemotherapy regimen course if not completed preoperatively, followed by endocrine therapy in patients with hormone receptor–positive disease (see page 135). Up to 1 year of total trastuzumab therapy should be completed if the tumor is HER2-positive (category 1). Capecitabine can be administered as a radiation sensitizer for patients at high risk for local recurrence (category 2B) if not given preoperatively. Endocrine therapy and trastuzumab can be administered concurrent with radiation therapy, if indicated. If capecitabine is administered as a radiation sensitizer, trastuzumab may be given concurrently.

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 on page 156.

Post-Therapy Surveillance and Follow-up

Post-therapy follow-up is optimally performed by members of the treatment team and includes the regular physical examinations and mammography. In patients undergoing breast-conserving therapy, the first follow-up mammogram should be performed 6 to 12 months after breast-conserving radiation therapy is completed (category 2B). The routine performance of alkaline phosphatase and liver function tests are not included in the guidelines.[192–194] In addition, the panel notes no evidence supporting the use of tumor markers for breast cancer, and that routine bone, CT, MRI, and PET scans, or ultrasound examinations in the asymptomatic patient provide no advantage in survival or ability to palliate recurrent disease and therefore are not recommended.[18,195]

The use of dedicated breast MRI may be considered as an option for post-therapy surveillance and follow-up in women at high risk for 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 compared with those with sporadic breast cancer.[196–198] (see NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian and Breast Cancer Screening and Diagnosis Guidelines).

The panel recommends that women with intact uteri who are taking tamoxifen undergo yearly gynecologic assessments and rapid evaluation of any vaginal spotting that might occur because of the risk for tamoxifen-associated endometrial carcinoma in postmenopausal women[199] (see page 136). 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 have 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.[200] 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.[201,202] 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 and venlafaxine seem to have only minimal effects on tamoxifen metabolism.

Premenopausal women who experience early ovarian failure secondary to adjuvant chemotherapy and postmenopausal women who are treated with an aromatase inhibitor are at increased risk for developing osteopenia or osteoporosis, with an associated increased risk for bone fracture. The guidelines thus recommend monitoring bone health during surveillance in these high-risk women[203] and encouraging the use of supplemental calcium and vitamin D (see page 136). Use of a bisphosphonate is generally the preferred intervention to improve or maintain bone mineral density for women with breast cancer and osteopenia or osteoporosis. A dental examination with preventive dentistry before initiating bisphosphonate therapy is recommended.

A special situation arises in women who are premenopausal at diagnosis, who develop amenorrhea during or after treatment, and for whom the use of an aromatase inhibitor is considered. The continuation or return after chemotherapy of ovarian function with or without amenorrhea has been documented.[160,161] 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 obtained if endocrine therapy with an aromatase inhibitor is initiated[161] (see page 151). Bilateral oophorectomy assures postmenopausal status in young women with therapy-induced amenorrhea and may be considered in these women 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 patient understanding of the benefits associated with regular administration of the medication.[204] The panel recommends implementing simple strategies to enhance patient adherence to endocrine therapy, such as direct questioning of the patient during office visits and brief, clear explanations of the value of taking the medication regularly and the therapeutic importance of longer durations of endocrine therapy (see page 136).

Stage IV Metastatic or Recurrent Breast Cancer

The staging evaluation of women who present with metastatic or recurrent breast cancer includes history and physical examination, CBC, 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 and pelvis, biopsy documentation of first recurrence if possible, and determination of hormone receptor (ER and PR) and HER2 status if not previously performed. The panel generally discourages PET or PET/CT scans for evaluating patients with recurrent disease, except when other staging studies are equivocal or suspicious (category 2B). Although only limited, mostly retrospective, evidence is available supporting the use of PET scanning to guide treatment planning through determining the extent of disease in select patients with recurrent or metastatic disease, [18,21,205,206] the panel considers biopsy of equivocal or suspicious sites more likely than PET scanning to provide accurate staging information in these patients. Genetic counseling may be recommended if patient is considered to be at high risk for hereditary breast cancer as defined by the NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Guidelines (available at www.nccn.org).

Local Disease Only

Patients with local recurrence only are divided into those who 1) were treated initially by mastectomy alone, 2) were treated with mastectomy with radiation therapy, and 3) underwent breast-conserving therapy (see page 137). Mastectomy-treated patients should undergo surgical resection of the local recurrence (if it can be accomplished without heroic surgery) and involved-field radiation therapy to chest and internal mammary nodes (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. Women whose disease recurs locally after initial breast-conserving therapy should undergo a total mastectomy and axillary lymph node dissection if not performed previously. After local treatment, women with local recurrences only should be considered for limited duration systemic chemotherapy or endocrine therapy similar to that outlined in the adjuvant chemotherapy section.

These guidelines include consideration of the addition of hyperthermia to irradiation for localized recurrences/metastasis (category 3; see page 137). Several prospective randomized trials have compared radiation with radiation plus hyperthermia in treating locally advanced/recurrent cancers, primarily breast cancer chest wall recurrences.[207,208] 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.[208] 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). The panel therefore recommends that the use of hyperthermia 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 treatment of systemic recurrence of breast cancer 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.[209]

Guideline Stratification for Therapy in Systemic Disease: Patients with recurrence of breast cancer or metastatic breast cancer at diagnosis are initially stratified according to whether bone metastasis is present (see section on Bisphosphonates). These 2 patient

subsets are then further stratified according to tumor hormone receptor and HER2 status (see page 137).

***Bisphosphonates*:** Bisphosphonate treatment is of value in patients with metastatic breast cancer in bone.[203,210] Women with bone metastasis, especially if lytic, should 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).[203,211–216] Bisphosphonates are given in addition to chemotherapy or endocrine therapy. Zoledronic acid may be superior to pamidronate in lytic breast metastasis.[217,218]

Extensive data from randomized trials support of the use of bisphosphonates for patients with metastatic disease to bone. Randomized clinical trial data include the use of zoledronic acid and pamidronate in the United States and ibandronate and clodronate in European countries.[212,213,218–223] In metastatic bone disease, bisphosphonate treatment is associated with fewer skeletal-related events and pathologic fractures, and less need for radiation therapy and surgery to treat bone pain.

The use of bisphosphonates 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 (i.e., endocrine therapy, chemotherapy or biologic therapy). Bisphosphonates should be accompanied by calcium and vitamin D supplementation with daily doses of calcium of 1200 to 1500 mg and vitamin D_3, 400 to 800 IU. Recommended agents in the United States are pamidronate, 90 mg, intravenously over 2 hours and 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 treatment can continue beyond that time.[223–225] The risk for renal toxicity necessitates serum creatinine monitoring before each dose is administered and dose reduction or discontinuation if renal function is reduced. Current clinical trial results support bisphosphonate use 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 patients with cancer documented an increased risk for jaw or facial bone surgery along with an increased risk for being diagnosed with 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 increased risk associated with an increase in cumulative dose of drug.[226]

A dental examination with preventive dentistry intervention is recommended before treatment with intravenous bisphosphonates, and dental procedures during treatment with intravenous bisphosphonates 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.[227]

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 intravenous bisphosphonate treatment is initiated in patients with metastatic disease. Frequent measurement of calcium, phosphorous, and magnesium may be prudent because hypophosphatemia and hypocalcemia have been reported.

***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 138). In postmenopausal women who have undergone 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 recurrent disease.[228,229] For postmenopausal women who are antiestrogen-naïve or are more than 1 year from previous antiestrogen therapy, the aromatase inhibitors seem to have superior outcome compared with tamoxifen, although the differences are modest.[230–233] 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 luteinizing hormone–releasing hormone (LHRH) agonists with endocrine therapy as for postmenopausal women. In premenopausal women without previous exposure to an antiestrogen, initial treatment involves antiestrogen alone, or ovarian suppression or ablation

plus endocrine therapy as for postmenopausal women (preferred;[234] see page 138).

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 140). Additional endocrine therapies for second-line and subsequent therapy are listed in the endocrine algorithm (see page 151).

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. It seems to be at least as effective as anastrozole in patients whose disease progressed on previous tamoxifen,[235,236] and a reanalysis of these studies suggests a longer duration of response favoring fulvestrant.[237] 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.[238] 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 the clinical benefit rates of exemestane and fulvestrant to be comparable (32.2% vs. 31.5%; $P = .853$).[239]

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 active in patients with negative ER and PR determinations, especially on the primary tumor and in soft tissue disease and/or bone-dominant disease.[240–242] 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 for 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 asymptomatic visceral disease, irrespective of HER2 tumor status (see page 139).

***Cytotoxic Chemotherapy*:** Women with hormone receptor–negative tumors not localized to the bone or soft tissue only or are associated with symptomatic visceral metastasis, or who have hormone receptor–positive tumors that are refractory to endocrine therapy, should undergo chemotherapy (see page 139). Various chemotherapy regimens are believed to be appropriate, as outlined in the treatment algorithm (see pages 152–155).

Combination chemotherapy generally provides higher rates of objective response and longer time to progression than single-agent chemotherapy. Combination chemotherapy is, however, associated with increased toxicity and provides little survival benefit.[243–246] 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 progression. Adverse effects may require dose reduction and cessation of chemotherapy before disease progression. Limited information suggests that progression-free survival can be prolonged with continuous chemotherapy versus shorter-course chemotherapy.[247,248] Because of the lack of overall survival differences, the decision to use prolonged versus shorter chemotherapy must be weighed against the detrimental effects of continuous chemotherapy on overall quality of life.

Single cytotoxic agents and combination chemotherapy regimens recommended by the panel for treating patients with metastatic disease are listed on pages 152 through 155. Single agents are categorized as either preferred or other based on a balance of the

efficacy, toxicity, and treatment schedules of the drugs. Likewise, combination regimens are 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); antimetabolites (capecitabine and gemcitabine); and non-taxane microtubule inhibitors (vinorelbine). Among preferred first-line combination regimens, the panel includes FAC/CAF; FEC; AC; EC; doxorubicin in combination with either docetaxel or paclitaxel (AT); CMF; docetaxel and capecitabine; and gemcitabine and paclitaxel. Under the heading of other single agents are cyclophosphamide, cisplatin, etoposide orally (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 152 –155).

A recent trial randomized 715 women with recurrent or metastatic breast cancer to first-line chemotherapy with paclitaxel with or without bevacizumab, a humanized monoclonal antibody against the vascular endothelial growth factor.[249] 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. No significant difference in overall survival was observed between the groups.

Ixabepilone, an epothilone B analogue, is a new agent for treating recurrent or metastatic breast cancer as a single agent (category 2A) or in combination with capecitabine (category 2B), both in the "other active options" grouping (see pages 152–155). Several phase II trials of women with metastatic breast cancer have evaluated ixabepilone as monotherapy: in a first-line setting in patients previously treated with anthracycline chemotherapy;[250] in patients with taxane-resistant metastatic breast cancer;[251] and in patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine.[252] In these trials, objective response rate, median duration of response, and median overall survival duration 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,[250] 12% (95% CI, 4.7%–26.5%), 10.4 months, and 7.9 months, respectively, for the taxane-resistant patients,[251] 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.[252]

Perez et al.[252] showed that grade 3/4 treatment-related toxicities included peripheral sensory neuropathy (14%) and neutropenia (54%). In addition, a phase III study compared ixabepilone plus capecitabine to capecitabine alone in women with metastatic breast cancer that progressed after anthracycline and taxane treatment.[253] The primary end point, progression-free survival, was 5.8 versus 4.2 months (HR, 0.75; 95% CI, 0.64–0.88; $P = .0003$), and the objective response rate was 35% versus 14% ($P < .0001$) in the 2 arms of the trial. No data on overall survival were reported, although the incidence of treatment-related death resulting from neutropenia was substantially higher in the combination arm.

Failure to achieve a tumor response 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 to respond to a chemotherapy regimen means the absence of even a marginal response to the use of a given chemotherapy regimen. Response to a chemotherapy regimen followed by progression of disease is not considered a failure to experience 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 (page 139). The panel recommends selecting patients for HER2-targeted therapy if their tumors are either positive for HER2 by FISH or 3+ by IHC. HER2 testing recommendations are described in the guidelines (see page 141). Patients with tumors IHC 0 or 1+ for HER2 or

FISH not amplified have very low rates of HER2-targeted response, and therapy with trastuzumab or lapatinib is not warranted.[254] Adequate standardization and validation of HER2 assays used in clinical practice is a concern, and data suggest that false-positive determinations are common.[29,31,34,35,255] Recommendations regarding HER2 testing have been published.[34,35]

In patients with metastatic breast cancer with HER2-positive tumors, first-line trastuzumab in combination with selected chemotherapeutics[48] or as a single agent[47,49] is recommended (see pages 152–155). Randomized trials show benefit from adding trastuzumab to other agents, including paclitaxel with or without carboplatin,[48,254,256,257] docetaxel,[257] and vinorelbine,[257] or using it as a single agent[49] 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.[258,259] 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.[48,260]

The panel recommends continuation of 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 after prior exposure to trastuzumab in the adjuvant setting. Several recent trials have shown benefit associated with continuing trastuzumab therapy after disease progression on a trastuzumab-containing regimen.[261–263] 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 involving an anthracycline and a taxane in either the metastatic or adjuvant setting.[264] 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; $P < .001$). 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 increased from 8.1 to 12 weeks ($P = .008$) with the combination.[265] The current guidelines include doses and schedules for representative chemotherapy single agents and regimens to use in combination with either trastuzumab or lapatinib for metastatic breast cancer, and for the combination of lapatinib and trastuzumab (see pages 152–155). Based on 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.[266] Generally this surgery should be undertaken only if complete local clearance of tumor may be obtained and other sites of disease are not immediately threatening to life. Alternatively, radiation therapy may be considered an option to surgery. Often this 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.[267–270] Substantial selection biases exist in all of these studies and are likely to confound the study results.[271,272] 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 of the breast (i.e., phylloides tumors, cystosarcoma phyllodes), and breast cancer during pregnancy can be found in the full breast cancer guidelines, available 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.[273,274] 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 6th 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, findings of 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 assign a diagnosis of IBC.[275,276] 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. There is a growing body of evidence that IBC patients, when compared with those with noninflammatory forms of locally advanced breast cancer, are more likely to have disease that is HER2-positive and hormone receptor–negative,[277,278] to have a less favorable prognosis[279,280] (i.e., disease-free survival at 5 years was 35% and 50% for inflammatory vs. noninflammatory status, respectively [$P = .020$][281]), and to be younger at disease presentation.[282] 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.[283,284] Nevertheless, current evidence provides justification for a separate guideline for the workup and treatment of patients diagnosed with IBC (see page 156).

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 involving a CBC 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). Evaluation of the 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.

The treatment of patients with IBC should involve a combined modality approach.[274] 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.[285] Results from a retrospective study of patients with IBC performed over 20 years at M. D. Anderson Cancer Center showed that initial treatment with doxorubicin-based chemotherapy followed by local therapy (i.e., radiation therapy or mastectomy, or both) and additional postoperative chemotherapy resulted in a 15-year disease-free survival rate of 28%.[286] 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.[287] A recent retrospective study has shown that addition of a taxane to an anthracycline-based regimen improved progression-free and overall survival in patients with ER-negative IBC.[288] A recent systematic review found evidence for an association between the intensity of preoperative therapy and the likelihood of a pathologic complete response.[289]

Primary surgical treatment of patients with IBC has been known for many years to be associated with very poor outcomes.[290] Use of 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 for mastectomy.

The panel recommends preoperative chemotherapy with an anthracycline-based regimen with or without taxanes for the initial treatment of patients with IBC (see page 156). Including 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 the completion of any planned chemotherapy (see page 156). Mastectomy is not recommended for patients with IBC who do not experience response to preoperative chemotherapy. Additional systemic chemotherapy and/or preoperative radiation should be considered for these patients, and those whose disease responds 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 (page 136–140).

***Axillary Breast Cancer*:** Axillary metastasis from an occult breast cancer represents approximately 3% to 5% of breast cancers. Evidence supporting recommendations on the management of these patients comes from a limited number of retrospective studies involving small numbers of patients[291–293] (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.[292,293]

Some evidence indicates that MRI of the breast can facilitate the 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%.[293] In addition, of the 7 patients with a negative MRI who subsequently underwent axillary lymph node dissection and radiation therapy to the whole breast, no evidence of local recurrence was evident at a median follow-up of 19 months.

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

Patients with MRI-positive disease should undergo further evaluation with ultrasound or MRI-guided biopsy and undergo treatment according to the clinical stage of the breast cancer. Treatment recommendations for those with MRI-negative disease are based on nodal status. For patients with T0,N1,M0 disease, options include either mastectomy plus axillary nodal dissection or axillary nodal dissection plus whole breast irradiation with or without nodal irradiation (see page 145). Systemic chemotherapy, endocrine therapy, or trastuzumab is given according to the recommendations for stage II or III disease (page 126). 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 (page 135).

Summary

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

With few exceptions, the evaluation, treatment, and follow-up recommendations in these guidelines are based on the results of past and present clinical trials. However, 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.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA Cancer J Clin 2008;58:71–96.

2. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687–1717.
3. Gail MH, Costantino JP, Bryant J, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. J Natl Cancer Inst 1999;91:1829–1846.
4. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med 1985;312:146–151.
5. White J, Morrow M, Moughan J, et al. Compliance with breast-conservation standards for patients with early-stage breast carcinoma. Cancer 2003;97:893–904.
6. Wilkinson NW, Shahryarinejad A, Winston JS, et al. Concordance with breast cancer pathology reporting practice guidelines. J Am Coll Surg 2003;196:38–43.
7. Giordano SH, Valero V, Buzdar AU, Hortobagyi GN. Efficacy of anastrozole in male breast cancer. Am J Clin Oncol 2002;25:235–237.
8. Giordano SH, Buzdar AU, Hortobagyi GN. Breast cancer in men. Ann Intern Med 2002;137:678–687.
9. Gundry KR. The application of breast MRI in staging and screening for breast cancer. Oncology (Williston Park) 2005;19:159–169; discussion 170, 173–154, 177.
10. Esserman L. Integration of imaging in the management of breast cancer. J Clin Oncol 2005;23:1601–1602.
11. 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.
12. Fischer U, Zachariae O, Baum F, et al. The influence of preoperative MRI of the breasts on recurrence rate in patients with breast cancer. Eur Radiol 2004;14:1725–1731.
13. Solin LJ, Orel SG, Hwang WT, et al. Relationship of breast magnetic resonance imaging to outcome after breast-conservation treatment with radiation for women with early-stage invasive breast carcinoma or ductal carcinoma in situ. J Clin Oncol 2008;26:386–391.
14. Members of the Breast Cancer Disease Site Group. Program in evidence-based care: a Cancer Care Ontario Program. Baseline staging tests in primary breast cancer. Practice guideline report #1-14. April 30, 2003. Available at: http://www.cancercare.on.ca/pdf/pebc1-14f.pdf. Accessed October 3, 2007.
15. Puglisi F, Follador A, Minisini AM, et al. Baseline staging tests after a new diagnosis of breast cancer: further evidence of their limited indications. Ann Oncol 2005;16:263–266.
16. Kumar R, Chauhan A, Zhuang H, et al. Clinicopathologic factors associated with false negative FDG-PET in primary breast cancer. Breast Cancer Res Treat 2006;98:267–274.
17. Wahl RL, Siegel BA, Coleman RE, Gatsonis CG. Prospective multicenter study of axillary nodal staging by positron emission tomography in breast cancer: a report of the staging breast cancer with PET study group. J Clin Oncol 2004;22:277–285.
18. Podoloff DA, Advani RH, Allred C, et al. NCCN Task Force Report: PET/CT scanning in cancer. J Natl Compr Canc Netw 2007;5(Suppl 1):S1–24.
19. Carr CE, Conant EF, Rosen MA, et al. The impact of FDG PET in the staging of breast cancer [abstract]. J Clin Oncol 2006:24:18 (Suppl 1):Abstract 530.
20. Khan QJ, O'Dea AP, Dusing R, et al. Integrated FDG-PET for initial staging of breast cancer [abstract]. J Clin Oncol 2007;25:18(Suppl 1):Abstract 558.
21. Rosen EL, Eubank WB. Mankoff DA. FDG PET, PET/CT, and breast cancer imaging. RadiGraphics 2007;27:S215–229.
22. Wang S, Saboorian MH, Frenkel E, et al. Laboratory assessment of the status of Her-2/neu protein and oncogene in breast cancer specimens: comparison of immunohistochemistry assay with fluorescence in situ hybridisation assays. J Clin Pathol 2000;53:374–381.
23. DAKO HercepTest [package insert]. Carpinteria, CA: DAKO Corp; 2004.
24. Pathway HER2 [package insert]. Tucson, AZ: Ventana Medical Systems, Inc.; 2004.
25. INFORM HER2/neu gene detection system [package insert]. Tucson, AZ: Ventana Medical Systems, Inc.; 2001.
26. PathVysion HER2/neu method [package insert]. Downers Grove, IL: Vysis, Inc.; 2001.
27. SPOT-Light HER2 CISH kit [package insert]. Camarillo, CA: Invitrogen Corp.; 2008.
28. Anderson S, Gilkerson E, Klein P. Concordance between local labs and a central lab using FISH and IHC for HER2 testing [abstract]. Breast Cancer Res Treat 2002;76:S68:Abstract 235.
29. Paik S, Bryant J, Tan-Chiu E, et al. Real-world performance of HER2 testing—National Surgical Adjuvant Breast and Bowel Project experience. J Natl Cancer Inst 2002;94:852–854.
30. Paik S, Tan-Chiu E, Bryant J, et al. Successful quality assurance program for HER2 testing in the NSABP trial for herceptin. Breast Cancer Res and Treat 2002;76(Suppl):S31.
31. Perez EA, Suman VJ, Davidson NE, et al. HER2 testing by local, central, and reference laboratories in specimens from the North Central Cancer Treatment Group N9831 Intergroup adjuvant trial. J Clin Oncol 2006;24:3032–3038.
32. Tubbs RR, Pettay JD, Roche PC, et al. Discrepancies in clinical laboratory testing of eligibility for trastuzumab therapy: apparent immunohistochemical false-positives do not get the message. J Clin Oncol 2001;19:2714–2721.
33. Press MF, Sauter G, Bernstein L, et al. Diagnostic evaluation of HER-2 as a molecular target: an assessment of accuracy and reproducibility of laboratory testing in large, prospective, randomized clinical trials. Clin Cancer Res 2005;11:6598–6607.
34. 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):S1–22.
35. Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 2007;25:118–147.
36. Cooke T, Reeves J, Lanigan A, Stanton P. HER2 as a prognostic and predictive marker for breast cancer. Ann Oncol 2001;12(Suppl 1):S23–28.
37. Paik S, Bryant J, Park C, et al. ErbB-2 and response to doxorubicin in patients with axillary lymph node-positive, hormone receptor-negative breast cancer. J Natl Cancer Inst 1998;90:1361–1370.
38. Paik S, Bryant J, Tan-Chiu E, et al. HER2 and choice of adjuvant chemotherapy for invasive breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-15. J Natl Cancer Inst 2000;92:1991–1998.
39. Piccart MJ, Di Leo A, Hamilton A. HER2 a 'predictive factor' ready to use in the daily management of breast cancer patients? Eur J Cancer 2000;36:1755–1761.
40. Thor AD, Berry DA, Budman DR, et al. erbB-2, p53, and efficacy of adjuvant therapy in lymph node-positive breast cancer. J Natl Cancer Inst 1998;90:1346–1360.

41. Pritchard KI, Shepherd LE, O'Malley FP, et al. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. N Engl J Med 2006;354:2103–2111.
42. Dressler LG, Berry DA, Broadwater G, et al. Comparison of HER2 status by fluorescence in situ hybridization and immunohistochemistry to predict benefit from dose escalation of adjuvant doxorubicin-based therapy in node-positive breast cancer patients. J Clin Oncol 2005;23:4287–4297.
43. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673–1684.
44. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659–1672.
45. Slamon D, Eiermann W, Robert N, et al. Phase III trial comparing AC-T with AC-TH and with TCH in the adjuvant treatment of HER2 positive early breast cancer patients: second interim efficacy analysis [abstract]. Presented at the San Antonio Breast Cancer Symposium; December 10–14, 2006; San Antonio, Texas. Abstract 52.
46. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006;354:809–820.
47. Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999;17:2639–2648.
48 Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783–792.
49. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002;20:719–726.
50. Allred DC, Harvey JM, Berardo M, et al. Prognostic and predictive factors in breast cancer by immunohistochemical analysis. Mod Pathol 1999;11:155–168.
51. Rhodes A, Jasani B, Barnes DM, et al. Reliability of immunochemical demonstration of oestrogen receptors in routine practice: interlaboratory variance in the sensitivity of detection and evaluation of scoring systems. J Clin Pathol 2000;53:125–130.
52. Rudiger T, Höfler H, Kreipe HH, et al. Quality assurance in immunohistochemistry: results of an interlaboratory trial involving 172 pathologists. Am J Surg Pathol 2002;26:873–882.
53. Arriagada R, Le MG, Rochard F, Contesso G. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institut Gustave-Roussy Breast Cancer Group. J Clin Oncol 1996;14:1558–1564.
54. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366:2087–2106.
55. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233–1241.
56. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227–1232.
57. McCormick B. Partial-breast radiation for early staged breast cancers: hypothesis, existing data, and a planned phase III trial. J Natl Compr Canc Netw 2005;3:301–307.
58. Pignol J-P, Olivotto E, Rakovitch WE, et al. Phase III randomized study of intensity modulated radiation therapy vs. standard wedging adjuvant breast radiotherapy. Int J Rad Oncol 2006;66:S1.
59. Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. J Natl Cancer Inst 2002;94:1143–1150.
60. Antonini N, Jones H, Horiot JC, et al. Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881–10882. Radiother Oncol 2007;82:265–271.
61. Bartelink H, Horiot JC, Poortmans P, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Engl J Med 2001;345:1378–1387.
62. Jones H, Antonini N, Colette L, et al. The impact of boost dose and margins on the local recurrence rate in breast conserving therapy: results from the EORTC boost-no-boost trial [abstract]. Int J Radiat Oncol Biol Phys 2007;69(3 Suppl):S2–3.
63. Fourquet A, Campana F, Zafrani B, et al. Prognostic factors of breast recurrence in the conservative management of early breast cancer: a 25 year follow-up. Int J Radiat Oncol Biol Phys 1989;17:719–725.
64. Komoike Y, Akiyama F, Iino Y, et al. Ipsilateral breast tumor recurrence (IBTR) after breast-conserving treatment for early breast cancer: risk factors and impact on distant metastases. Cancer 2006;106:35–41.
65. Zhou P, Gautam S, Recht A. Factors affecting outcome for young women with early stage invasive cancer treated with breast-conserving therapy. Breast Cancer Res Treat 2007;101:51–57.
66. Golshan M, Miron A, Nixon AJ, et al. The prevalence of germline BRCA1 and BRCA2 mutations in young women with breast cancer undergoing breast-conservation therapy. Am J Surg 2006;192:58–62.
67. Kroman N, Holtveg H, Wohlfahrt J, et al. Effect of breast-conserving therapy versus radical mastectomy on prognosis for young women with breast carcinoma. Cancer 2004;100:688–693.
68. Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med 2004;351:971–977.
69. Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer: a report of further follow-up. Presented at the San Antonio Breast Cancer Symposium; December 14, 2006; San Antonio, Texas. Abstract 11.
70. Fyles AW, McCready DR, Manchul LA, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med 2004;351:963–970.
71. Recht A, Come SE, Henderson IC, et al. The sequencing of chemotherapy and radiation therapy after conservative surgery for early-stage breast cancer. N Engl J Med 1996;334:1356–1361.
72. Dubey A, Recht A, Come SE, et al. Concurrent CMF and radiation therapy for early stage breast cancer: results of a pilot study. Int J Radiat Oncol Biol Phys 1999;45:877–884.
73. Markiewicz DA, Schultz DJ, Haas JA, et al. The effects of sequence and type of chemotherapy and radiation therapy on cosmesis and complications after breast conservation therapy. Int J Radiat Oncol Biol Phys 1996;35:661–668.
74. Abner AL, Recht A, Vicini FA, et al. Cosmetic results after surgery, chemotherapy, and radiation therapy for early breast cancer. Int J Radiat Oncol Biol Phys 1991;21:331–338.

75. Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol 2005;23: 7703–7720.

76. Bass SS, Lyman GH, McCann CR, et al. Lymphatic mapping and sentinel lymph node biopsy. Breast J 1999;5:288–295.

77. Cox CE. Lymphatic mapping in breast cancer: combination technique. Ann Surg Oncol 2001;8(9 Suppl):67S–70S.

78. Cox CE, Nguyen K, Gray RJ, et al. Importance of lymphatic mapping in ductal carcinoma in situ (DCIS): why map DCIS? Am Surg 2001;67:513–519; discussion 519–521.

79. Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer—a multicenter validation study. N Engl J Med 1998;339: 941–946.

80. McMasters KM, Giuliano AE, Ross MI, et al. Sentinel-lymph-node biopsy for breast cancer—not yet the standard of care. N Engl J Med 1998;339:990–995.

81. O'Hea BJ, Hill AD, El-Shirbiny AM, et al. Sentinel lymph node biopsy in breast cancer: initial experience at Memorial Sloan-Kettering Cancer Center. J Am Coll Surg 1998;186:423–427.

82. Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 2003;349:546–553.

83. Kuehn T, Vogl FD, Helms G, et al. Sentinel-node biopsy for axillary staging in breast cancer: results from a large prospective German multi-institutional trial. Eur J Surg Oncol 2004;30:252–259.

84. Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst 2006;98:599–609.

85. Dupont E, Cox C, Shivers S, et al. Learning curves and breast cancer lymphatic mapping: institutional volume index. J Surg Res 2001;97:92–96.

86. Cox CE, Salud CJ, Cantor A, et al. Learning curves for breast cancer sentinel lymph node mapping based on surgical volume analysis. J Am Coll Surg 2001;193:593–600.

87. Axelsson CK, Mouridsen HT, Zedeler K. Axillary dissection of level I and II lymph nodes is important in breast cancer classification. The Danish Breast Cancer Cooperative Group (DBCG). Eur J Cancer 1992;28A:1415–1418.

88. Kiricuta CI, Tausch J. A mathematical model of axillary lymph node involvement based on 1446 complete axillary dissections in patients with breast carcinoma. Cancer 1992;69:2496–2501.

89. Fisher B, Redmond C, Fisher ER, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med 1985;312: 674–681.

90. Alkuwari E, Auger M. Accuracy of fine-needle aspiration cytology of axillary lymph nodes in breast cancer patients. Cancer 2008;114: 89–93.

91. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998;16:2672–2685.

92. Bear HD, Anderson S, Smith RE, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Protocol B-27. J Clin Oncol 2006; 24:2019–2027.

93. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 2005;23:3676–3685.

94. Smith IE, Dowsett M, Ebbs SR, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol 2005;23:5108–5116.

95. Ellis MJ, Coop A, Singh B, et al. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol 2001; 19:3808–3816.

96. Hellman S. Stopping metastases at their source. N Engl J Med 1997;337:996–997.

97. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 1999;353:1641–1648.

98. Ragaz J, Olivotto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst 2005;97:116–126.

99. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 1997;337:949–955.

100. Recht A, Edge SB, Solin LJ, et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001;19:1539–1569.

101. Theriault R, Buzdar A, Hortobagyi G, et al. Irradiation (XRT) following mastectomy in patients treated with FAC adjuvant therapy—M.D. Anderson experience [abstract]. Proc Am Soc Clin Oncol 1998;17:99a. Abstract 381.

102. McGuire SE, Gonzolez-Angulo AM, Huang EH, et al. Postmastectomy radiation improves the outcome of patients with locally advanced breast cancer who achieve a pathologic complete response to neoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys 2007;68:1004–1009.

103. Huang EH, Tucker SL, Strom EA, et al. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. J Clin Oncol 2004; 22:4691–4699.

104. Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. Radiother Oncol 2007;82:247–253.

105. Nielsen HM, Overgaard M, Grau C, et al. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. J Clin Oncol 2006;24: 2268–2275.

106. Anderson, BO, Masetti, R, Silverstein, MJ, Oncoplastic approaches to the partial mastectomy: an overview of volume displacement techniques. Lancet Oncol 2005;6:145–157.

107. Huemer GM, Schrenk P, Moser F, et al. Oncoplastic techniques allow breast-conserving treatment in centrally located breast cancers. Plast Reconstr Surg 2007;120:390–398.

108. Malycha PL, Gough IR, Margaritoni M, et al. Oncoplastic breast surgery: a global perspective on practice, availability, and training. World J Surg 2008;32:2570–2577.

109. Kaur N, Petit JY, et al. Comparative study of surgical margins in oncoplastic surgery and quadrantectomy in breast cancer. Ann Surg Oncol 2005;12:539–545.

110. Loprinzi CL, Thome SD. Understanding the utility of adjuvant systemic therapy for primary breast cancer. J Clin Oncol 2001;19: 972–979.

111. Ravdin PM, Siminoff LA, Davis GJ, et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. J Clin Oncol 2001;19:980–991.

112. Olivotto IA, Bajdik CD, Ravdin PM, et al. Population-based validation of the prognostic model ADJUVANT! for early breast cancer. J Clin Oncol 2005;23:2716–2725.

113. Loprinzi CL, Ravdin PM. Decision-making for patients with early breast cancer: individualized decisions for and by patients and their physicians. J Natl Compr Canc Netw 2003;1:189–198.

114. Jeffrey SS, Lonning PE, Hillner BE. Genomics-based prognosis and therapeutic prediction in breast cancer. J Natl Compr Canc Netw 2005;3:291–300.

115. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001;98:10869–10874.

116. Perou CM, Jeffrey SS, van de Rijn M, et al. Distinctive gene expression patterns in human mammary epithelial cells and breast cancers. Proc Natl Acad Sci U S A 1999;96:9212–9217.

117. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A 2003;100:8418–8423.

118. Wang Y, Klijn JG, Zhang Y, et al. Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer. Lancet 2005;365:671–679.

119. van 't Veer LJ, Dai H, van de Vijver MJ, et al. Gene expression profiling predicts clinical outcome of breast cancer. Nature 2002;415:530–536.

120. van der Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 2002;347:1999–2009.

121. Glas AM, Floore A, Delahaye LJ, et al. Converting a breast cancer microarray signature into a high-throughput diagnostic test. BMC Genomics 2006;7:278–287.

122. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351:2817–2826.

123. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006;24:3726–3734.

124. Fan C, Oh DS, Wessels L, et al. Concordance among gene-expression-based predictors for breast cancer. N Engl J Med 2006; 355:560–569.

125. Swain SM, Wilson JW, Mamounas EP, et al. Estrogen receptor status of primary breast cancer is predictive of estrogen receptor status of contralateral breast cancer. J Natl Cancer Inst 2004;96:516–523.

126. Berry D, Cirrincione C, Henderson IC, et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. JAMA 2006;295:1658–1667.

127. Albain K, Barlow W, O'Malley F, et al. Concurrent (CAFT) versus sequential (CAF-T) chemohormonal therapy (cyclophosphamide, doxorubicin, 5-fluorouracil, tamoxifen) versus T alone for postmenopausal node positive estrogen (ER) and/or progesterone (PgR) receptor-positive breast cancer: mature outcomes and new biologic correlates on phase III Intergroup trial 0100 [meeting abstract]. Presented at the San Antonio Breast Cancer Symposium; December 8–11, 2004; San Antonio, Texas. Abstract LBA37.

128. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1998;351:1451–1467.

129. Berry DA, Muss HB, Thor AD, et al. HER-2/neu and p53 expression versus tamoxifen resistance in estrogen receptor-positive, node-positive breast cancer. J Clin Oncol 2000;18:3471–3479.

130. Eppenberger-Castori S, Kueng W, Benz C, et al. Prognostic and predictive significance of ErbB-2 breast tumor levels measured by enzyme immunoassay. J Clin Oncol 2001;19:645–656.

131. Knoop AS, Bentzen SM, Nielsen MM, et al. Value of epidermal growth factor receptor, HER2, p53, and steroid receptors in predicting the efficacy of tamoxifen in high-risk postmenopausal breast cancer patients. J Clin Oncol 2001;19:3376–3384.

132. Mass R. The role of HER-2 expression in predicting response to therapy in breast cancer. Semin Oncol 2000;27(Suppl):46–52; discussion 92–100.

133. Pegram MD, Pauletti G, Slamon DJ. HER-2/neu as a predictive marker of response to breast cancer therapy. Breast Cancer Res Treat 1998;52:65–77.

134. De Laurentiis M, Arpino G, Massarelli E, et al. A meta-analysis on the interaction between HER-2 expression and response to endocrine treatment in advanced breast cancer. Clin Cancer Res 2005;11:4741–4748.

135. Paik S, Shak S, Tang G, et al. Expression of the 21 genes in the Recurrence Score assay and tamoxifen clinical benefit in the NSABP study B-14 of node negative, estrogen receptor positive breast cancer [abstract]. J Clin Oncol 2005;23:16(Suppl 1): Abstract 510.

136. Arpino G, Green SJ, Allred DC, et al. HER-2 amplification, HER-1 expression, and tamoxifen response in estrogen receptor-positive metastatic breast cancer: a southwest oncology group study. Clin Cancer Res 2004;10:5670–5676.

137. Dowsett M, Allred C, Knox J, et al. Relationship between quantitative estrogen and progesterone receptor expression and human epidermal growth factor receptor 2 (HER2) status with recurrence in the Arimidex, Tamoxifen, Alone or in Combination trial. J Clin Oncol 2008;26:1059–1065.

138. Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomized controlled trial. Lancet 2007;369:559–570.

139. Kaufmann M, Jonat W, Hilfrich J, et al. Improved overall survival in postmenopausal women with early breast cancer after anastrozole initiated after treatment with tamoxifen compared with continued tamoxifen: the ARNO 95 study. J Clin Oncol 2007;25:2664–2670.

140. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst 2005;97:1262–1271.

141. Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol 2008;9:45–53.

142. Thurlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 2005;353:2747–2757.

143. Baum M, Budzar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet 2002;359: 2131–2139.

144. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365:60–62.

145. Duffy S, Jackson TL, Lansdown M, et al. The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) adjuvant breast cancer trial: first results of the endometrial sub-protocol following 2 years of treatment. Hum Reprod 2006;21:545–553.

146. Fallowfield L, Cella D, Cuzick J, et al. Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. J Clin Oncol 2004;22:4261–4271.

147. Eastell R, Adams JE, Coleman RE, et al. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. J Clin Oncol 2008;26:1051–1057.

148. Dowsett M, Cuzick J, Howell A, Jackson I. Pharmacokinetics of anastrozole and tamoxifen alone, and in combination, during adjuvant endocrine therapy for early breast cancer in postmenopausal women: a sub-protocol of the 'Arimidex and tamoxifen alone or in combination' (ATAC) trial. Br J Cancer 2001;85:317–324.

149. Buzdar AU, Guastalla JP, Nabholtz JM, et al. Impact of chemotherapy regimens prior to endocrine therapy: Results from the ATAC (Anastrozole and Tamoxifen, Alone or in Combination) trial. Cancer 2006;107:472–480.

150. Mouridsen H, Keshaviah A, Coates AS, et al. Cardiovascular adverse events during adjuvant endocrine therapy for early breast cancer using letrozole or tamoxifen: safety analysis of BIG 1-98 trial. 2007; J Clin Oncol 2007;25:5715–5722.

151. Boccardo F, Rubagotti A, Puntoni M, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial. J Clin Oncol 2005;23:5138–5147.

152. Boccardo F, Rubagotti A, Guglielmini P, et al. Switching to anastrozole versus continued treatment of early breast cancer. Updated results of the Italian Tamoxifen Anastrozole (ITA) trial. Ann Oncol 2006;17(Suppl 7):vii10–14.

153. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350:1081–1092.

154. Jakesz R, Jonat W, Gnant M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet 2005;366:455–462.

155. Jonat W, Gnant M, boccardo F, et al. Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. Lancet Oncol 2006;7:991–996.

156. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003;349:1793–1802.

157. Goss PE, PE, Ingle JN, Pater JL, et al. Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen. J Clin Oncol 2008;26:1948–1955.

158. Whelan TJ, Goss PE, Ingle JN, et al. Assessment of quality of life in MA.17: a randomized, placebo-controlled trial of letrozole after 5 years of tamoxifen in postmenopausal women. J Clin Oncol 2005;23:6931–6940.

159. Perez EA, Josse RG, Pritchard KI, et al. Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: a companion study to NCIC CTG MA.17. J Clin Oncol 2006;24:3629–3635.

160. Braverman AS, Sawhney H, Tendler A, et al. Pre-menopausal serum estradiol (E2) levels may persist after chemotherapy (CT)-induced amenorrhea in breast cancer (BC) [abstract]. Proc Am Soc Clin Oncol 2002;21:Abstract 164.

161. Smith IE, Dowsett M, Yap YS, et al. Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. J Clin Oncol 2006;24:2444–2447.

162. Erban JK, Lau J. On the toxicity of chemotherapy for breast cancer—the need for vigilance. J Natl Cancer Inst 2006;98: 1096–1097.

163. Early Breast Cancer Trialists' Collaborative Group Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet 1998;352:930–942

164. Wood WC, Budman DR, Korzun AH, et al. Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. N Engl J Med 1994;330:1253–1259.

165. Menard S, Valagussa P, Pilotti S, et al. Response to cyclophosphamide, methotrexate, and fluorouracil in lymph node-positive breast cancer according to HER2 overexpression and other tumor biologic variables. J Clin Oncol 2001;19:329–335.

166. Muss HB, Thor AD, Berry DA, et al. c-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer. N Engl J Med 1994;330:1260–1266.

167. Bang SM, Heo DS, Lee KH, et al. Adjuvant doxorubicin and cyclophosphamide versus cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy in premenopausal women with axillary lymph node positive breast carcinoma. Cancer 2000;89:2521–2526.

168. Fisher B, Anderson S, Tan-Chiu E, et al. Tamoxifen and chemotherapy for axillary node-negative, estrogen receptor-negative breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-23. J Clin Oncol 2001;19:931–942.

169. Fisher B, Brown AM, Dimitrov NV, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. J Clin Oncol 1990; 8:1483–1496.

170. Fisher B, Anderson S, Wickerham DL, et al. Increased intensification and total dose of cyclophosphamide in a doxorubicin-cyclophosphamide regimen for the treatment of primary breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-22. J Clin Oncol 1997;15:1858–1869.

171. Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 2003;21:976–983.

172. Mamounas EP, Bryant J, Lembersky B, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. J Clin Oncol 2005;23:3686–3696.

173. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus

concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21:1431–1439.

174. Levine MN, Pritchard KI, Bramwell VH, et al. Randomized trial comparing cyclophosphamide, epirubicin, and fluorouracil with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer: update of National Cancer Institute of Canada Clinical Trials Group Trial MA5. J Clin Oncol 2005;23:5166–5170.

175. French Adjuvant Study Group. Benefit of a high-dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French Adjuvant Study Group 05 randomized trial. J Clin Oncol 2001;19:602–611.

176. Piccart MJ, Di Leo A, Beauduin M, et al. Phase III trial comparing two dose levels of epirubicin combined with cyclophosphamide with cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. J Clin Oncol 2001;19:3103–3110.

177. Roche H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 trial. J Clin Oncol 2006;24:5664–5671.

178. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 2005;352:2302–2313.

179. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 2008;358: 1663–1671.

180. Sparano JA, Wang M, Martino S, et al. Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node negative breast cancer [abstract]. Presented at the San Antonio Breast Cancer Symposium; December 8–11, 2005; San Antonio, Texas. Abstract 48.

181. Jones S, Holmes F, O'Shaughnessey J, et al. Extended follow-up and analysis of the US Oncology Adjuvant trial 9735: docetaxel/cyclophosphamide is associated with an overall survival benefit compared to doxorubicin/cyclophosphamide and is well-tolerated in women 65 or older. San Antonio Breast Cancer Symposium; December 13–16, 2007; San Antonio, Texas. Abstract 12.

182. Burstein HJ. The distinctive nature of HER2-positive breast cancers. N Engl J Med 2005;353:1652–1654.

183. Perez EA, Romond EH, Suman VJ, et al. Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer [abstract]. J Clin Oncol 2007;25(Suppl 1):Abstract 512.

184. Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol 2005;23:7811–7819.

185. Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North American Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol 2008;26:1231–1238.

186. Geyer CE, Bryant JL, Romond MS, et al. Update of cardiac dysfunction on NSABP-31, a randomized trial of sequential doxorubicin/cyclophosphamide (AC) → paclitaxel (T) vs. AC → T with trastuzumab (H). J Clin Oncol 2006;24(Suppl 1): Abstract 581.

187. Telli ML, Hunt SA, Carlson RW, Guardino AE. Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. J Clin Oncol 2007;25:3525–3533.

188. Smith I, Procter M, Gelber RD, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomized controlled trial. Lancet 2007:369:29–36.

189. Norris B, Chia S, Cheang M , et al. Poor 10 yr breast cancer specific survival and relapse free survival for HER2-positive T1pN0 tumors. San Antonio Breast Cancer Symposium; December 10–14, 2006; San Antonio, Texas. Abstract 2031.

190. Untch M, Gelber RD, Jackisch C, et al. Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial. Ann Oncol 2008;19:1090–1096.

191. Hortobagyi GN, Singletary SE, Strom EA. Locally advanced breast cancer. In: Harris JR, Lippman ME, Morrow M, Osborne CK, eds. Diseases of the Breast. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.

192. Rosselli Del Turco M, Palli D, Cariddi A, et al. Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. National Research Council Project on Breast Cancer Follow-Up. JAMA 1994;271:1593–1597.

193. Smith TJ, Davidson NE, Schapira DV, et al. American Society of Clinical Oncology 1998 update of recommended breast cancer surveillance guidelines. J Clin Oncol 1999;17:1080–1082.

194. The GIVIO Investigators. Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. JAMA 1994;271:1587–1592.

195. Bast RC Jr, Ravdin P, Hayes DF, et al. 2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001;19:1865–1878.

196. Kirova YM, Stoppa-Lyonnet D, Savignoni A, et al. Risk of breast cancer recurrence and contralateral breast cancer in relation to BRCA1 and BRCA2 mutation status following breast-conserving surgery and radiotherapy. Eur J Cancer 2005;41:2304–2311.

197. Pierce LJ, Levin AM, Rebbeck TR, et al. Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. J Clin Oncol 2006; 24:2437–2443.

198. Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2004;22:2328–2335.

199. American College of Obstetrics and Gynecology Committee on Gynecologic Practice. ACOG Committee Opinion. No. 336: tamoxifen and uterine cancer. Obstet Gynecol 2006;107:1475–1478.

200. Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 2000;356:2059–2063.

201. Garber K. Tamoxifen pharmacogenetics moves closer to reality. J Natl Cancer Inst 2005;97:412–413.

202. Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst 2005;97:30–39.

203. Hillner BE, Ingle JN, Chlebowski RT, et al. American Society of Clinical Oncology 2003 Update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 2003;21:4042–4057.

204. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487–497.

205. Eubank WB, Mankoff D, Bhattacharya M, et al. Impact of FDG PET on defining the extent of disease and on the treatment of patients

with recurrent or metastatic breast cancer. AJR Am J Roentgenol 2004;183:479–486.

206. Moon DH, Maddahi J, Silverman DH, et al. Accuracy of whole-body fluorine-18-FDG PRT for the detection of recurrent or metastatic breast carcinoma. J Nucl Med 1998;39:431–435.

207. Vernon CC, Hand JW, Field SB, et al. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials. International Collaborative Hyperthermia Group. Int J Radiat Oncol Biol Phys 1996;35:731–744.

208. Jones EL, Oleson JR, Prosnitz LR, et al. Randomized trial of hyperthermia and radiation for superficial tumors. J Clin Oncol 2005;23:3079–3085.

209. Higgins MJ, Wolff AC. Therapeutic options in the management of metastatic breast cancer. Oncology 2008;22:614–623; discussion 623, 627–629.

210. Theriault RL, Biermann JS, Brown E, et al. NCCN Task Force Report: Bone Health and Cancer Care. J Natl Compr Canc Netw 2006;(4 Suppl 2):S1–20.

211. Conte PF, Latreille J, Mauriac L, et al. Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial. The Aredia Multinational Cooperative Group. J Clin Oncol. 1996;14:2552–2559.

212. Hortobagyi GN, Theriault RL, Lipton A, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. J Clin Oncol 1998;16:2038–2044.

213. Theriault RL, Lipton A, Hortobagyi GN, et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. J Clin Oncol 1999;17:846–854.

214. Berenson JR, Rosen LS, Howell A, et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. Cancer 2001;91:1191–1200.

215. Ali SM, Esteva FJ, Hortobagyi G, et al. Safety and efficacy of bisphosphonates beyond 24 months in cancer patients. J Clin Oncol 2001;19:3434–3437.

216. Theriault RL. The role of bisphosphonates in breast cancer. J Natl Compr Canc Netw 2003;1:232–241.

217. Rosen LS, Gordon D, Kaminski M, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. Cancer J 2001; 7:377–387.

218. Rosen LS, Gordon DH, Dugan W Jr, et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer 2004;100:36–43.

219. Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. Cancer 2000;88:1082–1090.

220. Hortobagyi GN, Theriault RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. N Engl J Med 1996; 335:1785–1971.

221. Diel IJ, Body JJ, Lichinitser MR, et al. Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. Eur J Cancer 2004;40:1704–1712.

222. McLachlan SA, Cameron D, Murray R, et al. Safety of oral ibandronate in the treatment of bone metastases from breast cancer: long-term follow-up experience. Clin Drug Investig 2006;26:43–48.

223. Pecherstorfer M, Rivkin S, Body JJ, et al. Long-term safety of intravenous ibandronic acid for up to 4 years in metastatic breast cancer: an open-label trial. Clin Drug Investig 2006; 26:315–322.

224. Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. Cancer 2000;88:1082–1090.

225. Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. Cancer 2003;98:1735–1744.

226. Wilkinson GS, Kuo YF, Freeman JL, Goodwin JS. Intravenous bisphosphonate therapy and inflammatory conditions or surgery of the jaw: a population-based analysis. J Natl Cancer Inst 2007; 99:1016–1024.

227. Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. Systematic Review Bisphosphonates Osteonecrosis of the Jaw. Ann Intern Med 2006; 144:753–761.

228. Buzdar A, Douma J, Davidson N, et al. Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. J Clin Oncol 2001;19:3357–3366.

229. Buzdar AU, Jonat W, Howell A, et al. Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma: results of a survival update based on a combined analysis of data from two mature phase III trials. Arimidex Study Group. Cancer 1998;83:1142–1152.

230. Bonneterre J, Thurlimann B, Robertson JF, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. J Clin Oncol 2000;18:3748–3757.

231. Nabholtz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. J Clin Oncol 2000; 18:3758–3767.

232. Vergote I, Bonneterre J, Thurlimann B, et al. Randomised study of anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women. Eur J Cancer 2000;36(Suppl 4): S84–85.

233. Paridaens R, Therasse P, Dirix L, et al. First line hormonal treatment (HT) for metastatic breast cancer (MBC) with exemestane (E) or tamoxifen (T) in postmenopausal patients (pts)—a randomized phase III trial of the EORTC Breast Group [abstract]. J Clin Oncol 2004;22:14S (Suppl 1):Abstract 515.

234. Klijn JG, Blamey RW, Boccardo F, et al. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol 2001;19: 343–353.

235. Osborne CK, Pippen J, Jones SE, et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus

anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. J Clin Oncol 2002;20:3386–3395.

236. Howell A, Robertson JF, Quaresma Albano J, et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. J Clin Oncol 2002;20:3396–3403.

237. Robertson JF, Osborne CK, Howell A, et al. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: a prospective combined analysis of two multicenter trials. Cancer 2003;98:229–238.

238. Ingle JN, Suman VJ, Rowland KM, et al. Fulvestrant in women with advanced breast cancer after progression on prior aromatase inhibitor therapy: North Central Cancer Treatment Group Trial N0032. J Clin Oncol 2006;24:1052–1056.

239. Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. J Clin Oncol 2008;26:1664–1670.

240. Lonning PE, Bajetta E, Murray R, et al. Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: a phase II trial. J Clin Oncol 2000;18 :2234–2244.

241. Dombernowsky P, Smith I, Falkson G, et al. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. J Clin Oncol 1998; 16:453–461.

242. Buzdar A, Jonat W, Howell A, et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. J Clin Oncol 1996;14:2000–2011.

243. Carrick S, Parker S, Wilcken N, et al. Single agent versus combination chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev 2005;2:CD003372.

244. Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an Intergroup trial (E1193). J Clin Oncol 2003;21:588–592.

245. O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 2002;20:2812–2823.

246. Albain K, Nag S, Calderillo-Ruiz J, et al. Global phase III study of gemcitabine plus paclitaxel (GT) vs. paclitaxel (T) as frontline therapy for metastatic breast cancer. (MBC): First report of overall survival [abstract]. J Clin Oncol 2004;22:14s(Suppl 1):Abstract 510.

247. Muss HB, Case LD, Richards F II, et al. Interrupted versus continuous chemotherapy in patients with metastatic breast cancer. The Piedmont Oncology Association. N Engl J Med 1991:325;1342–1348.

248. Falkson G, Gelman R, Pandya K, et al. Eastern Cooperative Oncology Group randomized trials of observation versus maintenance therapy for patients with metastatic breast cancer in complete remission following induction treatment. J Clin Oncol 1998;16:1669–1676.

249. Miller KD, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007;357:2666–2676.

250. Roche H, Yelle L, Cognetti F, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, as first-line therapy in patients with metastatic breast cancer previously treated with anthracycline chemotherapy. J Clin Oncol 2007;25: 3415–3420.

251. Thomas E, Tabernero J, Fornier M, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, in patients with taxane-resistant metastatic breast cancer. J Clin Oncol 2007;25:3399–3406.

252. Perez EA, Lerzo G, Pivot X, et al. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. J Clin Oncol 2007;25:3407–3414.

253. Thomas ES, Gomez HL, Li RK, et al. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. J Clin Oncol 2007;25:5210–5217.

254. Seidman AD, Berry D, Cirrincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER2 overexpressors and random assignment to trastuzumab or not in HER2 nonoverexpressors: final results of Cancer and Leukemia Groups B protocol 9840. J Clin Oncol 2008;26:1642–1649.

255. Roche PC, Suman VJ, Jenkins RB, et al. Concordance between local and central laboratory HER2 testing in the breast Intergroup trial N9831. J Natl Cancer Inst 2002;94:855–857.

256. Robert N, Leyland-Jones B, Asmar K, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER2-overexpressing metastatic breast cancer. J Clin Oncol 2006;24:2786–2792.

257. Burstein HJ, Keshaviah A, Baron AD, et al. Trastuzumab plus vinorelbine or taxane chemotherapy for HER2-overexpressing metastatic breast cancer: the trastuzumab and vinorelbine or taxane study. Cancer 2007;110:965–972.

258. Yamamoto D, Iwase S, Kitamura K, et al. A phase II study of trastuzumab and capecitabine for patients with HER2-overexpressing metastatic breast cancer: Japan Breast Cancer Research Network 00 trial. Cancer Chemother Pharmacol 2008;61: 509–514.

259. Schaller G, Bangemann, N, Weber J, et al. Efficacy and safety of trastuzumab plus capecitabine in a German multicentre phase II study of pre-treated metastatic breast cancer [abstract]. J Clin Oncol 2005;23:18(Suppl 1):Abstract 717.

260. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 2002;20: 1215–1221.

261. Bartsch R, Wenzel C, Altorjai G, et al. Capecitabine and trastuzumab in heavily pretreated metastatic breast cancer. J Clin Oncol 2007;25:3853–3858.

262. Von Minckwitz G, Vogel P, Schmidt M, et al. Trastuzumab treatment beyond progression in patients with HER2 positive metastatic breast cancer—interim report [abstract]. J Clin Oncol 2008; 26(Suppl 1):Abstract 4056.

263. Von Minckwitz G, Zielinski C, Maarteense E, et al. Capecitabine vs. Capecitabine + trastuzumab in patients with HER2-positive metastatic breast cancer progressing during trastuzumab treatment: the TBP phase III study (GBG 26/BIG 3-05) [abstract]. J Clin Oncol 2008;26(Suppl 1):Abstract 1025.

264. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355:2733–2743.

265. O'Shaughnessy J, Blackwell KL, Burstein H, et al. A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on

trastuzumab therapy [abstract]. J Clin Oncol 2008;26(Suppl 1): Abstract 1015.

266. Hortobagyi GN. Multidisciplinary management of advanced primary and metastatic breast cancer. Cancer 1994;74:416–423.

267. Khan SA, Stewart AK, Morrow M. Does aggressive local therapy improve survival in metastatic breast cancer? Surgery 2002;132: 620–627.

268. Babiera GV, Rao R, Feng L, et al. Effect of primary tumor extirpation in breast cancer patients who present with stage IV disease and an intact primary tumor. Ann Surg Oncol 2006;13:776–782.

269. Rapiti E, Verkooijen HM, Vlastos G, et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. J Clin Oncol 2006;24:2743–2749.

270. Rao R, Feng L, Kuerer HM, et al. Timing of surgical intervention for the intact primary in stage IV breast cancer patients. Ann Surg Oncol 2008;15:1696–1702.

271. Morrow M, Goldstein LJ. Surgery of the primary tumor in metastatic breast cancer: closing the barn door after the horse has bolted? J Clin Oncol 2006;24:2694–2696.

272. Olson JA, Marcom PK. Benefit or bias? The role of surgery to remove the primary tumor in patients with metastatic breast cancer. Ann Surg 2008;247:739–740.

273. Jaiyesimi IA, Buzdar AU, Hortobagyi G. Inflammatory breast cancer: a review. J Clin Oncol 1992;10:1014–1024.

274. Dawood S, Cristofanilli M. What progress have we made in managing inflammatory breast cancer? Oncology 2007;21:673–687.

275. Greene FL, Page DL, Fleming ID, et al. AJCC Cancer Staging Manual. 6th ed. New York, NY: Springer-Verlag; 2002.

276. Haagensen CD. Inflammatory carcinoma. In: Haagensen CD, ed. Diseases of the Breast. Philadelphia, PA: WB Saunders, 1956: pp 488–498.

277. Paradiso A, Tommasi S, Brandi M, et al. Cell kinetics and hormonal receptor status in inflammatory breast carcinoma. Comparison with locally advanced disease. Cancer 1989;1:1922–1927.

278. Turpin E, Bièche I, Bertheau P, et al. Increased incidence of ERBB2 overexpression and TP53 mutation in inflammatory breast cancer. Oncogene 2002;21:7593–7597.

279. Cristofanilli M, Valero V, Buzdar AU, et al. Inflammatory breast cancer (IBC) and patterns of recurrence: understanding the biology of a unique disease. Cancer 2007;110.1436–1444.

280. Panades M, Olivotto IA, Speers CH, et al. Evolving treatment strategies for inflammatory breast cancer: a population-based survival analysis. J Clin Oncol 23:1941–1950.

281. Merajver SD, Weber BL, Cody R, et al. Breast conservation and prolonged chemotherapy for locally advanced breast cancer: The University of Michigan experience. J Clin Oncol 1997;15:2873–2881.

282. Hance KW, Anderson WF, Devesa SS, et al. Trends in inflammatory breast carcinoma incidence and survival: the Surveillance, Epidemiology, and End Results Program at the National Cancer Institute. J Natl Cancer Instit 2005;97:966–975.

283. Nguyen DM, Sam K, Tsimelzon A, et al. Molecular heterogeneity of inflammatory breast cancer; a hyperproliferative phenotype. Clin Cancer Res 2006;12:5047–5054.

284. Bleicher RJ, Morrow M. What progress have we made in managing inflammatory breast cancer? The Dawood/Cristofanilli article reviewed. Oncology 2007;21:679–680.

285. Fleming RY, Asmar L, Buzdar AU, et al. Effectiveness of mastectomy by response to induction chemotherapy for control in inflammatory breast cancer. Ann Surg Oncol 1997;4:452–461.

286. Ueno NT, Buzdar AU, Singletary SE, et al. Combined-modality treatment of inflammatory breast carcinoma: twenty years of experience at M. D. Anderson Cancer Center. Cancer Chemother Pharmacol 1997;40:321–324.

287. Therasse P, Mauriac L, Welnicka-Jaskiewicz M, et al. Final results of a randomized phase III trial comparing cyclophosphamide, epirubicin, and fluorouracil with a dose-intensified epirubicin and cyclophosphamide plus filgrastim as neoadjuvant treatment in locally advanced breast cancer: an EORTC-NCIC-SAKK Multicenter Study. J Clin Oncol 2003;21:843–850.

288. Cristofanilli M, Gonzalez-Angulo AM, Buzdar AU, et al. Paclitaxel improves the prognosis in estrogen receptor negative inflammatory breast cancer: the M. D. Anderson Cancer Center experience. Clin Breast Cancer 2004;4:415–419.

289. Kim T, Lau J, Erban J. Lack of uniform diagnostic criteria for inflammatory breast cancer limits interpretation of treatment outcomes: a systematic review. Clin Breast Cancer 2006;7:386–395.

290. Kell MR, Morrow M. Surgical aspects of inflammatory breast cancer. Breast Dis 2005–2006;22:67–73.

291. Blanchard DK, Shetty PB, Hilsenbeck SG, Elledge RM. Association of surgery with improved survival in stage IV breast cancer patients. Ann Surg 2008;247:732–738.

292. Varadarajan R, Edge SB, Yu J, et al. Prognosis of occult breast carcinoma presenting as isolated axillary nodal metastasis. Oncology 2006;71:456–459.

293. Olson JA, Morris EA, Van Zee KJ, et al. Magnetic resonance imaging facilitates breast conservation for occult breast cancer. Ann Surg Oncol 2000;7:411–415.

Individual Financial Disclosures for the NCCN Breast Cancer Panel

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