

National Comprehensive  
Cancer Network<sup>®</sup>

# Breast Cancer

Version 2.2002

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**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.

To find clinical trials online at NCCN member institutions, [click here: nccn.org/clinical\\_trials/physician.html](#)

**NCCN Categories of Consensus:** All recommendations are Category 2A unless otherwise specified.

See [NCCN Categories of Consensus](#)

DIAGNOSIS

WORK-UP

PRIMARY TREATMENT

RISK REDUCTION

SURVEILLANCE/FOLLOW-UP

Lobular carcinoma  
in situ (LCIS)<sup>a</sup>  
Stage 0  
Tis, N0, M0

- H&P
- Diagnostic bilateral mammogram
- Pathology review

Observation

Counseling regarding consideration of tamoxifen for risk reduction (category 1, see also [NCCN Breast Cancer Risk Reduction Guidelines](#))  
or  
In special circumstances, bilateral mastectomy ± reconstruction may be considered for risk reduction

- Interval history and physical exam every 6-12 mo
- Mammogram every 12 mo, unless postbilateral mastectomy
- If treated with tamoxifen, monitor per [NCCN Breast Cancer Risk Reduction Guidelines](#)

<sup>a</sup>[See NCCN Breast Cancer Screening Guidelines.](#)

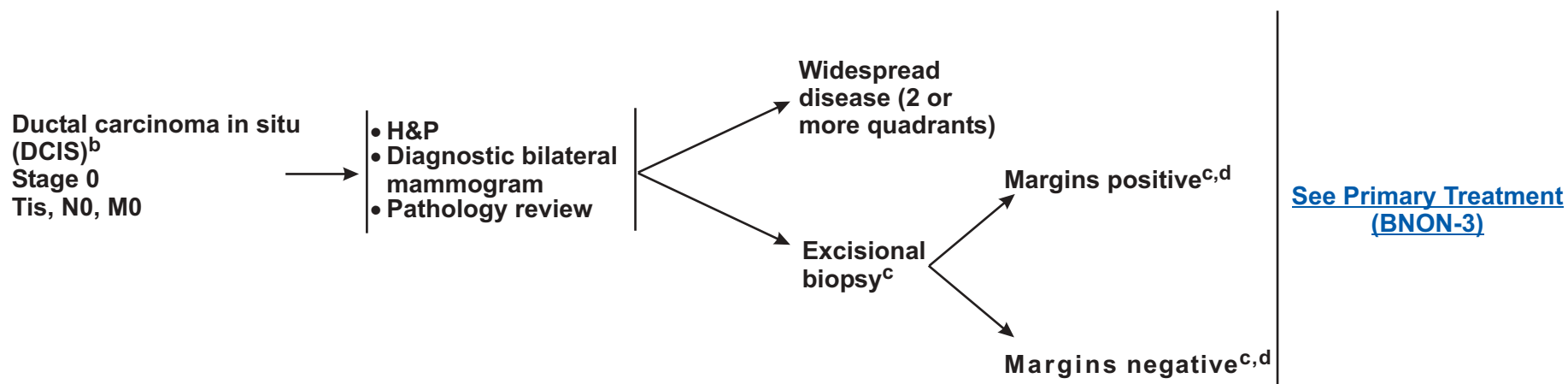
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BNON-1

## DIAGNOSIS

## WORK-UP



<sup>b</sup>Clinical trial participation in this situation is especially important.

<sup>c</sup>Re-resection(s) may be performed in effort to obtain negative margins in patients desiring breast conserving therapy. Patients not amenable to margin-free excision should have total mastectomy.

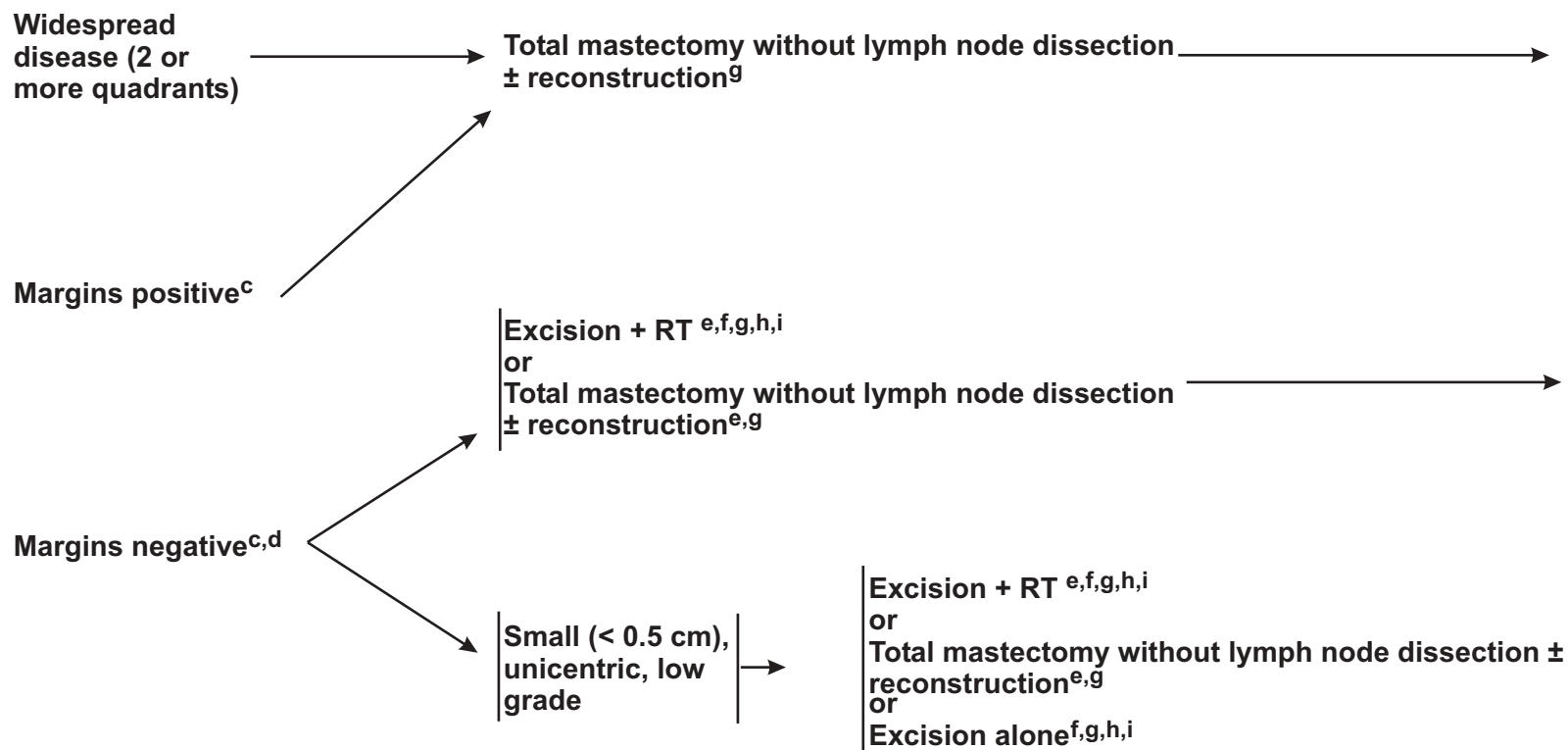
<sup>d</sup>[See margin status in DCIS \(BNON-A\).](#)

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**BNON-2**

## PRIMARY TREATMENT



<sup>c</sup>Re-resection(s) may be performed in effort to obtain negative margins in patients desiring breast conserving therapy. Patients not amenable to margin-free excision should have total mastectomy.

<sup>d</sup>[See margin status in DCIS \(BNON-A\).](#)

<sup>e</sup>Long-term survival with mastectomy versus excision and irradiation appears to be approximately equivalent.

<sup>f</sup>Complete resection should be documented by analysis of margins, specimen mammography and post-excision mammography. (Post-excision mammography is Category 3).

<sup>g</sup>Patients found to have invasive disease at total mastectomy or re-excision should be managed as stage I or stage II disease, including lymph node staging.

<sup>h</sup>[See Contraindications to Breast-Conserving Therapy \(BNON-B\).](#)

<sup>i</sup>There are selected patients with DCIS that may be appropriately treated with excision without irradiation. Criteria for patient selection relate to the patient's acceptance for potential increased risk of local recurrence, age, and comorbidity, tumor size, grade, and margin.

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**BNON-3**

## DCIS POSTSURGICAL TREATMENT

## SURVEILLANCE/FOLLOW-UP

**Adjuvant treatment:**

Consider tamoxifen for 5 years for:

- Patients treated with breast-conserving therapy (lumpectomy) and RT (category 1)<sup>j</sup>
- Patients treated with excision alone<sup>j</sup>

**Risk reduction therapy:**

- Counseling regarding consideration of tamoxifen for risk reduction. [See also NCCN Breast Cancer Risk Reduction Guidelines \(category 2B\)](#)

- Interval history and physical exam every 6 mo for 5 yr, then annually
- Mammogram every 12 mo
- If treated with tamoxifen, monitor per [NCCN Breast Cancer Risk Reduction Guidelines](#)

<sup>j</sup>Tamoxifen provides risk reduction in the ipsilateral breast treated with breast conservation and in the contralateral breast in patients with mastectomy or breast conservation. Since a survival advantage has not been demonstrated, individual consideration of risks and benefits is important ([See also NCCN Breast Cancer Risk Reduction Guidelines](#)).

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BNON-4

## Margin Status in DCIS

**Substantial controversy exists regarding the definition of a negative pathologic margin in DCIS. Controversy arises out of the heterogeneity of the disease, difficulties in distinguishing the spectrum of hyperplastic conditions, anatomic considerations of the location of the margin, and inadequate prospective data on prognostic factors in DCIS. Margins greater than 10 mm are widely accepted as negative (but may be excessive and may lead to a less optimal cosmetic outcome). Margins less than 1 mm are considered inadequate. Insufficient data are available to make definitive statements regarding margins between 1 and 10 mm.**

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**BNON-A**

## CONTRAINDICATIONS FOR BREAST-CONSERVING THERAPY REQUIRING RADIATION THERAPY

Contraindications for breast-conserving therapy requiring radiation therapy include:

**Absolute:**

- Prior RT to the breast or chest wall
- RT during pregnancy
- Diffuse suspicious or malignant appearing microcalcifications
- Multicentric disease

**Relative:**

- Multifocal disease requiring two or more separate surgical incisions.
- Connective tissue disease especially scleroderma
- Tumors > 5 cm (category 2B)

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**BNON-B**

**CLINICAL  
STAGE**

**WORK-UP**

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

- H&P
- CBC, platelets
- Liver function tests
- Chest x-ray
- Diagnostic bilateral mammogram, ultrasound as necessary
- Pathology review
- Determination of tumor ER/PR status and HER-2 status<sup>a</sup>
- Breast MRI with dedicated breast coil for cases equivocal for breast conserving therapy (optional)
- Bone scan (optional) (should be done if localized symptoms or elevated alkaline phosphatase)

[See  
Locoregional  
Treatment  
\(BINV-2\)](#)

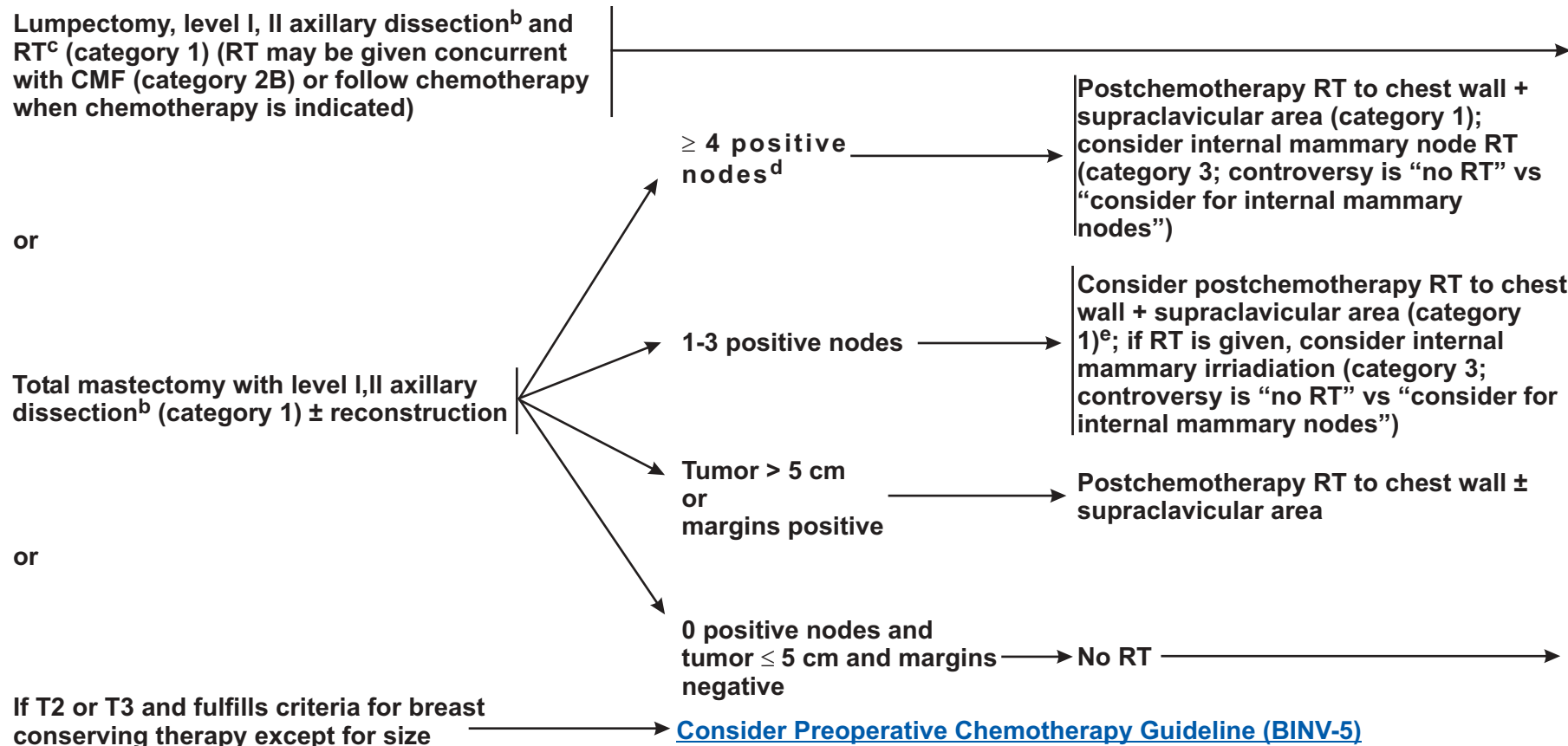
<sup>a</sup>HER-2 testing should be done using IHC and/or FISH. An IHC result of 2+ should be confirmed by FISH.

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**BINV-1**

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



[See Systemic Adjuvant Treatment \(BINV-3\)](#)

<sup>b</sup>See [Surgical Axillary Staging \(BINV-A\)](#) and [Axillary Dissection \(BINV-B\)](#).

<sup>c</sup>See [Contraindications to Breast-Conserving Therapy \(BINV-C\)](#).

<sup>d</sup>Consideration may be given to additional staging including abdominal CT/US/MRI; chest CT (category 2B).

<sup>e</sup>There is contradictory high-level evidence on survival benefit in this subset and risk of local recurrence is low in the absence of RT.

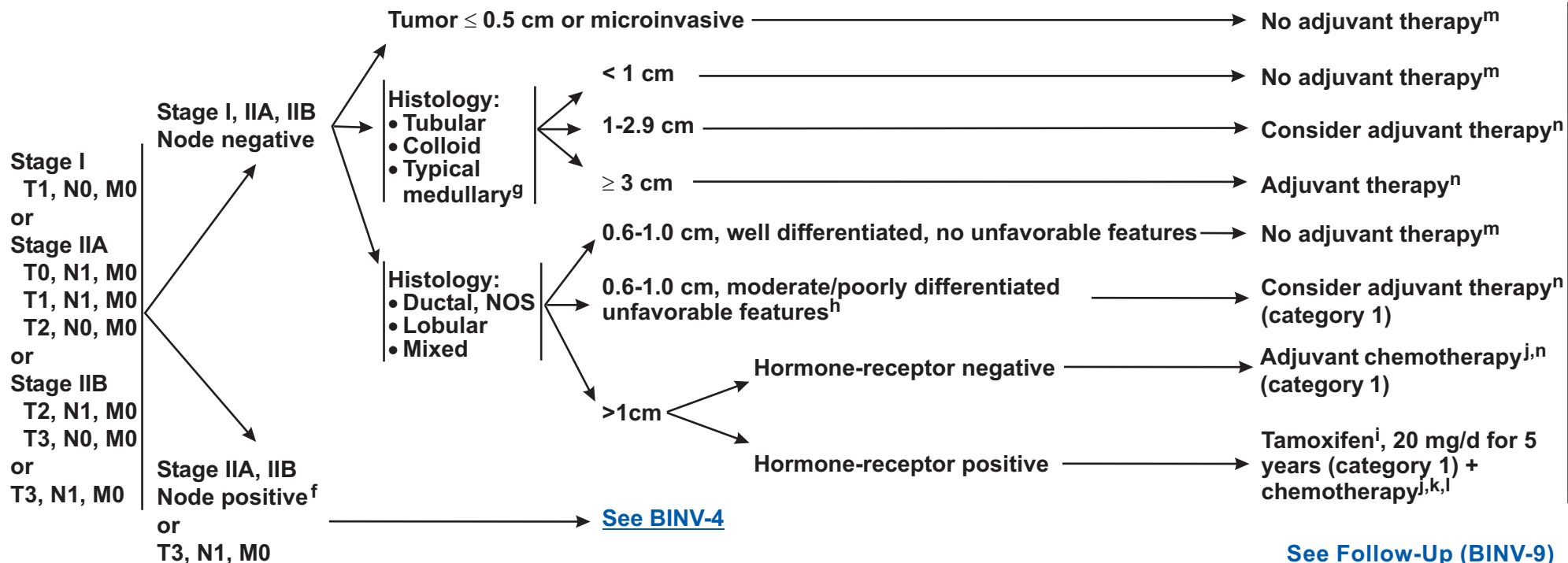
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**BINV-2**

## SYSTEMIC ADJUVANT TREATMENT



[See Follow-Up \(BINV-9\)](#)

<sup>f</sup>The panel awaits the completion/maturation of the randomized trials of high-dose therapy in women with 4 or more involved axillary lymph nodes.

<sup>g</sup>[See Classification of typical medullary carcinoma \(BINV-D\).](#)

<sup>h</sup>Angiolymphatic invasion, high nuclear grade, high histologic grade, HER-2 overexpression, hormone receptor negative (category 2B).

<sup>i</sup>[See discussion of early data on anastrozole for postmenopausal, hormone receptor positive patients \(BINV-E\).](#)

<sup>j</sup>There are insufficient data to make chemotherapy recommendations for those over 70 yrs old. Treatment should be individualized with consideration of comorbid conditions.

<sup>k</sup>The benefits of chemotherapy and of tamoxifen are additive. However, the absolute benefit from chemotherapy may be small. The decision to add chemotherapy to tamoxifen should be individualized, especially in those with a favorable prognosis and in older women where the incremental benefit of chemotherapy may be small.

<sup>l</sup>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. Early evidence suggests similar benefits from ovarian suppression (i.e. LHRH agonist or antagonist) as from ovarian ablation. The benefit of ovarian ablation/suppression in premenopausal women who have received adjuvant chemotherapy is uncertain.

<sup>m</sup>If ER+ consider tamoxifen for risk reduction and to diminish the small risk of disease recurrence.

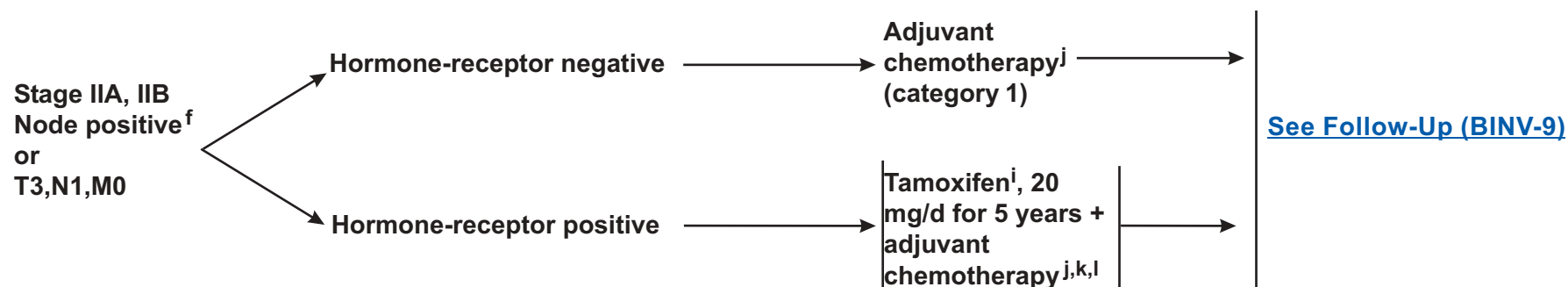
<sup>n</sup>[See Adjuvant Chemotherapy \(BINV-F\).](#) See also [NCCN Breast Cancer Risk Reduction Guideline.](#)

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**BINV-3**

## SYSTEMIC ADJUVANT TREATMENT



<sup>f</sup>The panel awaits the completion/maturation of the randomized trials of high-dose therapy in women with 4 or more involved axillary lymph nodes.

<sup>i</sup>[See discussion of early data on anastrozole for postmenopausal, receptor-positive patients \(BINV-E\).](#)

<sup>j</sup>There are insufficient data to make chemotherapy recommendations for those over 70 yrs old. Treatment should be individualized with consideration of comorbid conditions.

<sup>k</sup>The benefits of chemotherapy and of tamoxifen are additive. However, the absolute benefit from chemotherapy may be small. The decision to add chemotherapy to tamoxifen should be individualized, especially in those with a favorable prognosis and in older women where the incremental benefit of chemotherapy may be small.

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<sup>n</sup>[See Adjuvant Chemotherapy \(BINV-F\).](#) See also [NCCN Breast Cancer Risk Reduction Guideline.](#)

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**BINV-4**

## Preoperative Chemotherapy Guideline

### CLINICAL STAGE

### WORK-UP

Stage IIA  
T2, N0, M0  
or  
Stage IIB  
T2, N1, M0  
T3, N0, M0  
and  
fulfills criteria  
for breast  
conserving surgery  
except for tumor size

- H&P
- CBC, platelets
- Liver function tests
- Diagnostic bilateral mammogram, ultrasound as necessary
- Chest x-ray
- Pathology review
- Determination of tumor ER/PR status and HER-2 status if tumor tissue available<sup>a</sup>
- Breast MRI with dedicated breast coil for cases equivocal for breast conserving therapy (optional)
- Bone scan (optional) (category 2B) (should be done if localized symptoms or elevated alkaline phosphatase)

Stage IIIA  
T3, N1, M0  
and  
fulfills criteria  
for breast  
conserving surgery  
except for tumor size

- H&P
- CBC, platelets
- Liver function tests
- Diagnostic bilateral mammogram, ultrasound as necessary
- Chest x-ray
- Pathology review
- Determination of tumor ER/PR status and HER-2 status if tumor tissue available<sup>a</sup>
- Breast MRI with dedicated breast coil for cases equivocal for breast conserving therapy (optional)
- Bone scan (category 2B)
- Abdominal CT or US or MRI (category 2B)

[See Primary Treatment \(BINV-6\)](#)

<sup>a</sup>HER-2 testing should be done using IHC and/or FISH. An IHC result of 2+ should be confirmed by FISH.

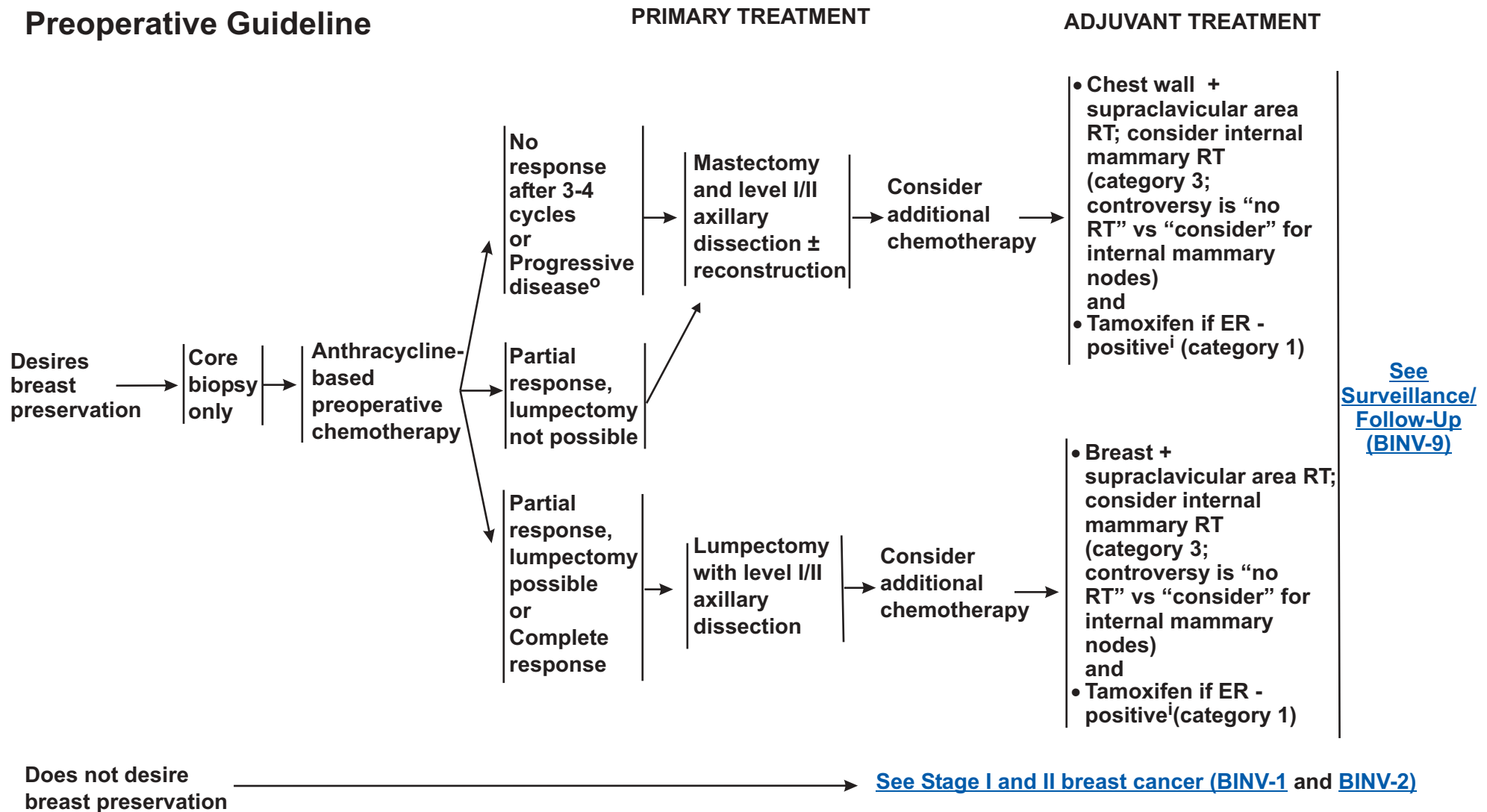
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**Note:** All recommendations are category 2A unless otherwise indicated.

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**BINV-5**

## Preoperative Guideline



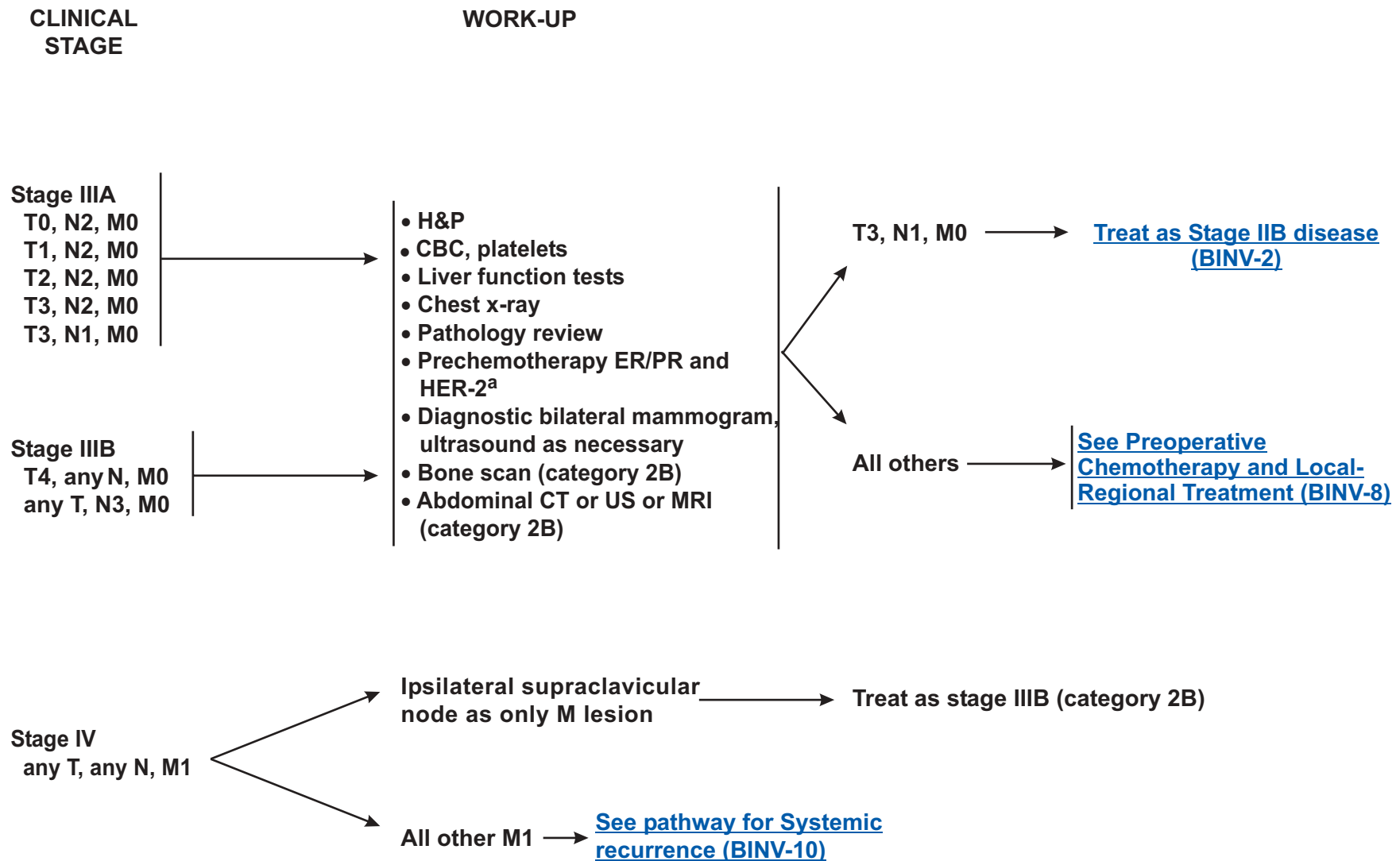
[See discussion of early data on anastrozole for postmenopausal, hormone receptor positive patients \(BINV-E\).](#)

<sup>o</sup>If there is progressive disease after any course of therapy or no response after a minimum of 3 cycles, proceed to mastectomy.

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**BINV-6**



<sup>a</sup>HER-2 testing should be done using IHC and/or FISH. An IHC result of 2+ should be confirmed by FISH.

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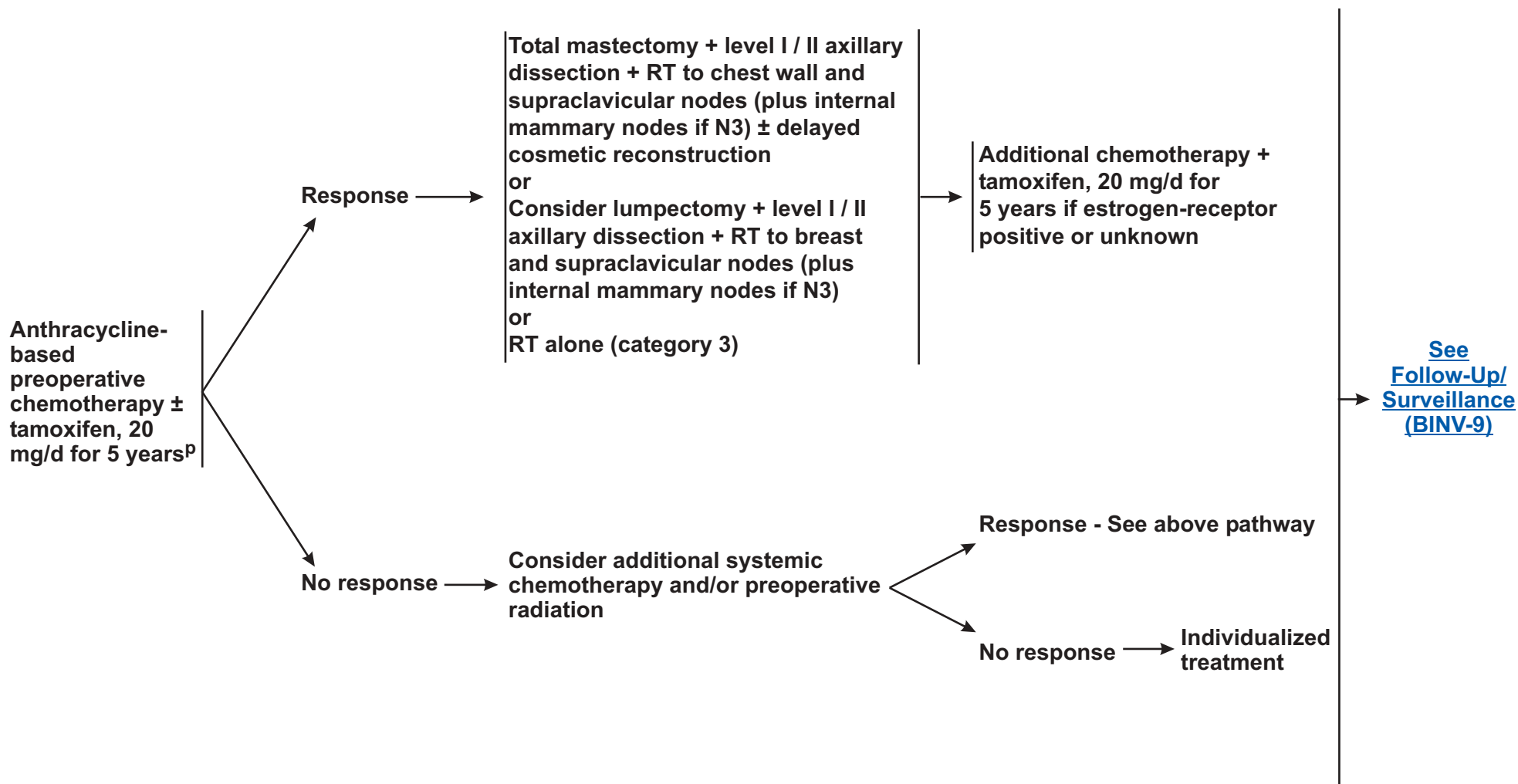
**Note:** All recommendations are category 2A unless otherwise indicated.  
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**BINV-7**

**PREOPERATIVE CHEMOTHERAPY**

**LOCAL-REGIONAL TREATMENT**

**ADJUVANT TREATMENT**



<sup>P</sup>At every stage, clinical trials are appropriate. These are situations in which participation in clinical trials such as high dose chemotherapy is appropriate.

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**BINV-8**

**SURVEILLANCE/  
FOLLOW-UP**

- Interval history and physical exam every 4-6 mo for 5 yr, then every 12 mo
- Mammogram every 12 mo (and 6 mo post-RT if breast conserved) (category 2B)
- Women on tamoxifen: pelvic exam every 12 mo if uterus present

**RECURRENCE WORK-UP  
or  
INITIAL WORK-UP FOR  
STAGE IV DISEASE**

- H&P
- CBC, platelets
- Liver function tests
- Chest x-ray
- Bone scan
- X-rays of symptomatic bones and long and weight-bearing bones abnormal on bone scan
- Consider CT or MRI of chest and abdomen
- Biopsy documentation of first recurrence, if possible
- If not previously performed, HER-2 testing should be done using IHC and/or FISH. An IHC result of 2+ should be confirmed by FISH.

Local  
disease  
only

Systemic  
disease<sup>q</sup>

[See Treatment of  
Recurrence/Stage IV  
\(BINV-10\)](#)

<sup>q</sup>Pamidronate should be given (category 1) in addition to chemotherapy or hormonal therapy if osteolytic lesions, expected survival ≥ 3 months, and creatinine < 2.5 mg/dL.

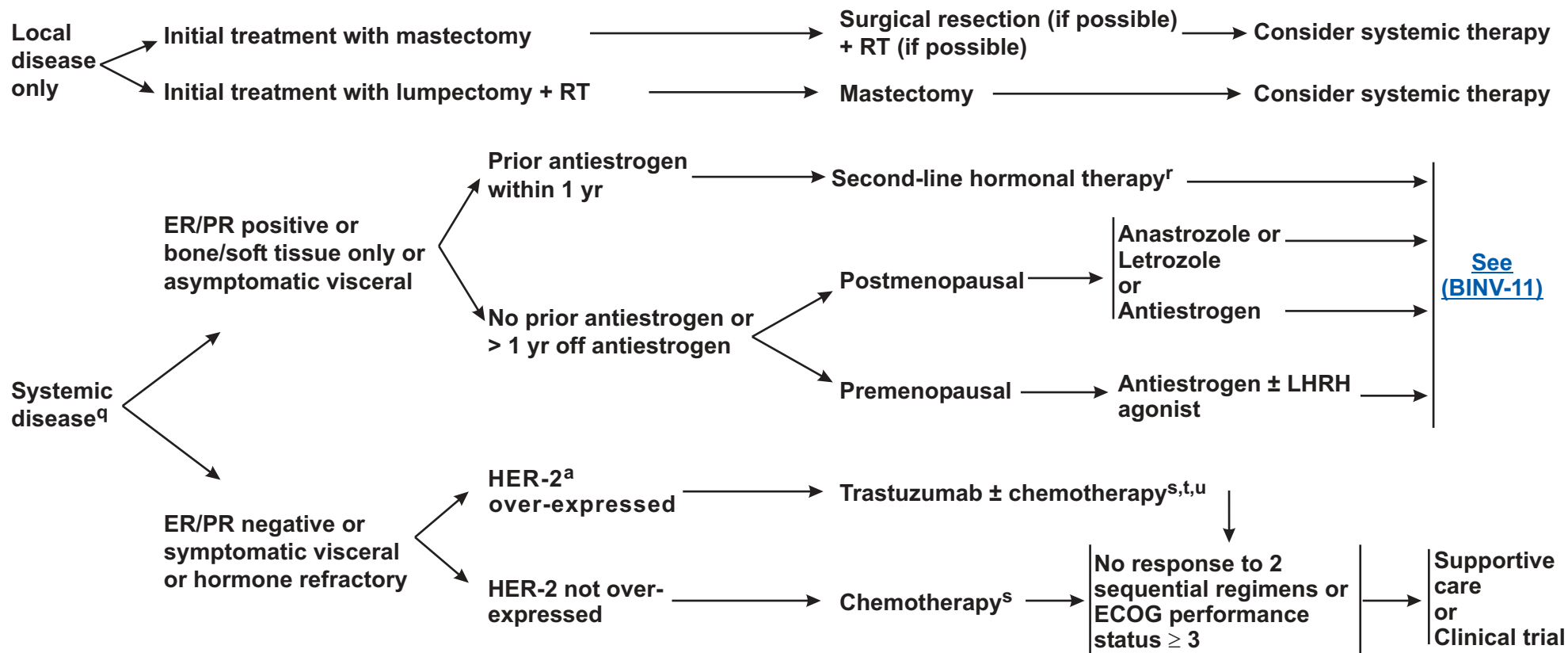
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**BINV-9**

## TREATMENT OF RECURRENCE/STAGE IV



<sup>a</sup>HER-2 testing should be done using IHC and/or FISH. An IHC result of 2+ should be confirmed by FISH.

<sup>q</sup>Pamidronate should be given (category 1) in addition to chemotherapy or hormonal therapy if osteolytic lesions, expected survival  $\geq 3$  months, and creatinine  $< 2.5$  mg/dL.

<sup>r</sup>See [Subsequent Hormonal Therapy \(BINV-G\)](#).

<sup>s</sup>See [Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer \(BINV-H\)](#)

<sup>t</sup>A single randomized trial is available supporting the addition of trastuzumab to paclitaxel. Early non-randomized data are available supporting the addition of such agents as docetaxel, vinorelbine, and platinum compounds in combination with trastuzumab.

<sup>u</sup>Trastuzumab given in combination with AC is associated with significant cardiac toxicity.

### TREATMENT OF RECURRENCE

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

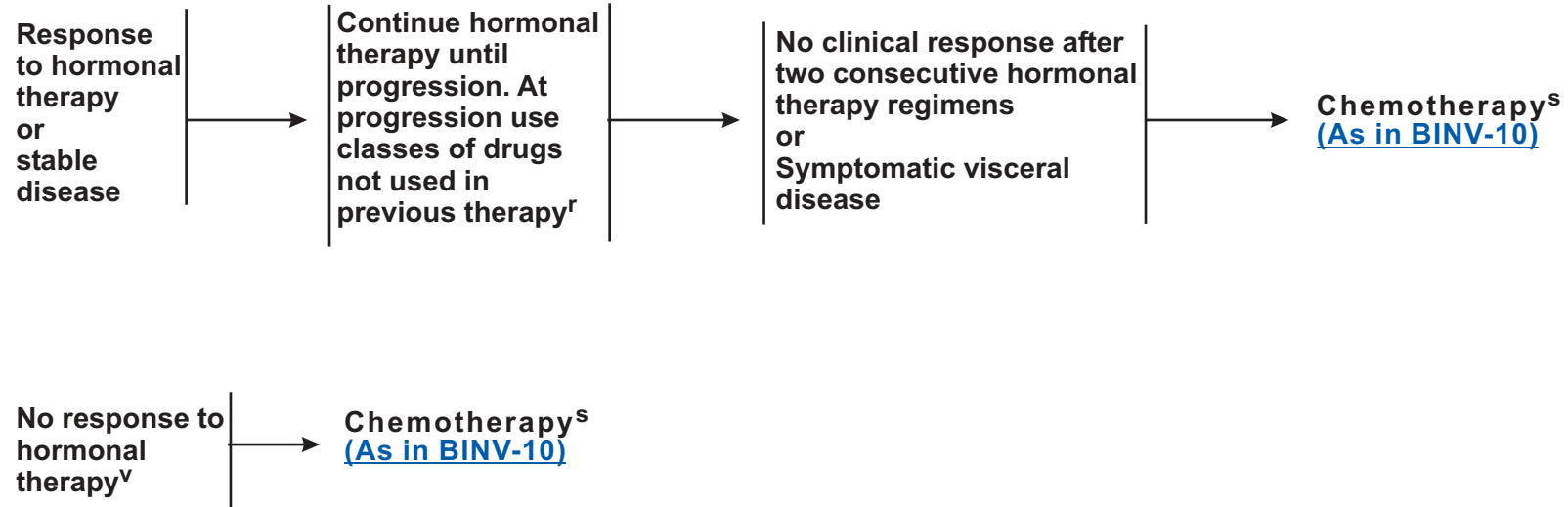
- |                           |   |
|---------------------------|---|
| 1. Brain metastases       | 7. Ureteral obstruction                           |
| 2. Leptomeningeal disease | 8. Impending pathologic fracture                  |
| 3. Choroid metastases     | 9. Pathologic fracture                            |
| 4. Pleural effusion       | 10. Cord compression                              |
| 5. Pericardial effusion   | 11. Localized painful bone or soft-tissue disease |
| 6. Biliary obstruction    |   |

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**BINV-10**

## FOLLOW-UP THERAPY FOR HORMONE TREATMENT OF RECURRENCE/STAGE IV



### TREATMENT OF RECURRENCE

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

- |                           |   |
|---------------------------|---|
| 1. Brain metastases       | 7. Ureteral obstruction                           |
| 2. Leptomeningeal disease | 8. Impending pathologic fracture                  |
| 3. Choroid metastases     | 9. Pathologic fracture                            |
| 4. Pleural effusion       | 10. Cord compression                              |
| 5. Pericardial effusion   | 11. Localized painful bone or soft-tissue disease |
| 6. Biliary obstruction    |   |

<sup>r</sup>See [Subsequent Hormonal Therapy \( BINV-G\)](#).

<sup>s</sup>See [Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer \(BINV-H\)](#).

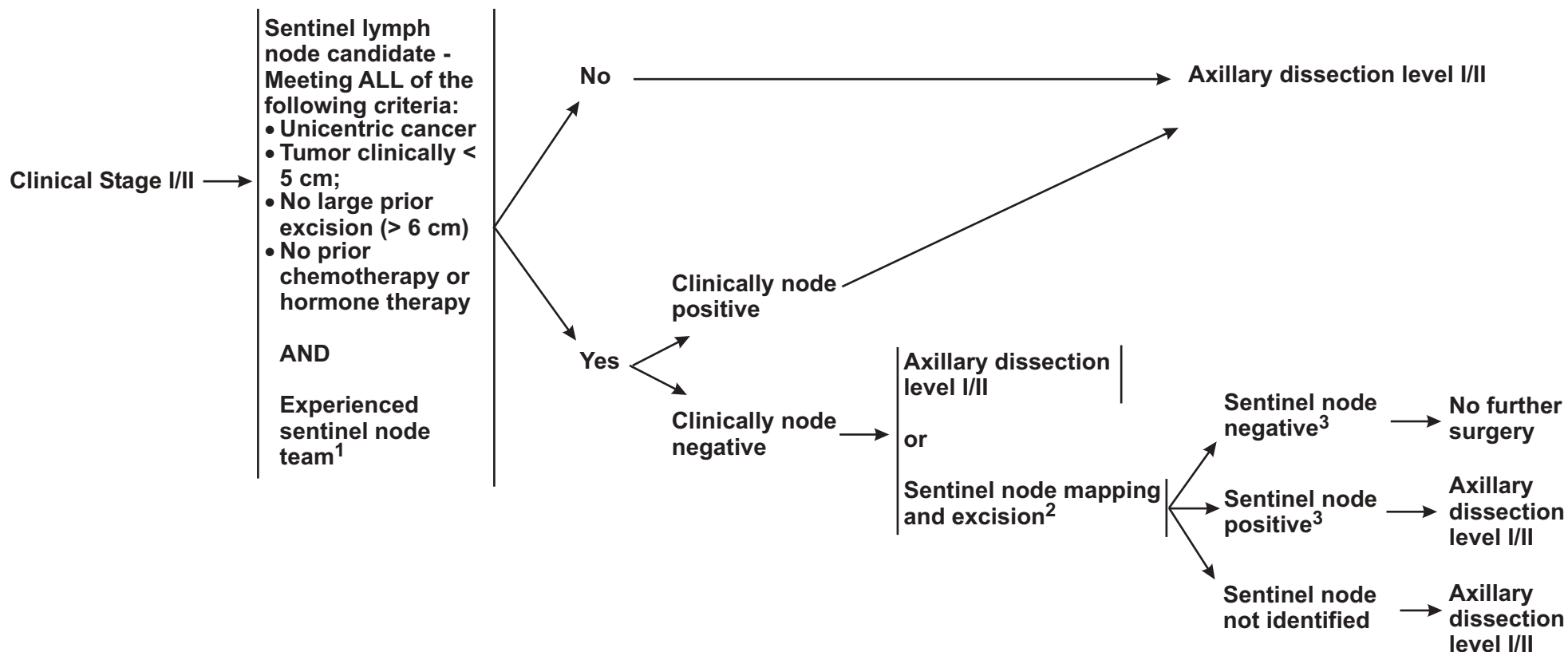
<sup>v</sup>Consideration may be given to further hormone therapy in patients failing to respond to first-line hormone therapy and whose disease is indolent, and for those patients achieving a response to chemotherapy and in whom the decision is made to discontinue chemotherapy.

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**BINV-11**

## Surgical Axillary Staging - Stage I, IIA, and IIB



<sup>1</sup>Sentinel node team must have documented experience with SNB 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.

<sup>2</sup>Axillary sentinel node biopsy in all cases; Internal mammary sentinel node biopsy optional if drainage maps to internal mammary nodes (Category 3).

<sup>3</sup>Sentinel node involvement defined by multilevel node sectioning with hematoxylin and eosin staining. Cytokeratin Immunohistochemistry (IHC) may be used for equivocal cases on H&E. Routine cytokeratin IHC to define node involvement is controversial (Category 3).

[Return to Locoregional Treatment \(BINV-2\)](#)

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**BINV-A**

## AXILLARY DISSECTION

In the absence of definitive data demonstrating superior survival from the performance of axillary lymph node dissection, patients who have particularly favorable tumors, patients for whom the selection of adjuvant systemic therapy is unlikely to be affected, for the elderly, or those 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 I or II nodes.

Sentinel lymph node biopsy may be considered an option (category 2B) if there is an experienced sentinel node team and the patient is an appropriate sentinel lymph node biopsy candidate ([See BINV-A](#)).

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**BINV-B**

## CONTRAINDICATIONS TO BREAST-CONSERVING THERAPY REQUIRING RADIATION THERAPY

Contraindications for breast-conserving therapy requiring radiation therapy include:

**Absolute:**

- Prior RT to the breast or chest wall
- RT during pregnancy
- Diffuse suspicious or malignant appearing microcalcifications
- Multicentric disease

**Relative:**

- Multifocal disease requiring two or more separate surgical incisions.
- Connective tissue disease especially scleroderma
- Tumors > 5 cm (category 2B)

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**BINV-C**

## PROPER CLASSIFICATION OF TYPICAL MEDULLARY CARCINOMA

**Proper classification of typical medullary carcinoma as distinguished from atypical medullary carcinoma or non-medullary carcinoma is critical. Both atypical medullary carcinoma and non-medullary carcinoma exhibit particularly aggressive biological behavior while typical medullary carcinoma does not. (Jensen, 1997). The medullary carcinoma classification systems of Ridolfi (Ridolfi, 1997) and Tavassoli (Tavassoli, 1992) are recommended.**

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**Note:** All recommendations are category 2A unless otherwise indicated.

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

**BINV-D**

## DISCUSSION OF EARLY DATA ON ANASTROZOLE FOR POSTMENOPAUSAL, HORMONE RECEPTOR POSITIVE PATIENTS

Early evidence from a single, large, double-blind, randomized clinical trial demonstrates that anastrozole provides superior disease free survival and a favorable toxicity profile compared to tamoxifen as adjuvant therapy for hormone receptor-positive breast cancer in postmenopausal women. Additional follow-up of this trial and additional experience is required before definitive conclusions can be made. At the current time, anastrozole may be considered as an option to tamoxifen after discussion of the available data between the physician and patient. These data do not address whether women currently on tamoxifen should be changed to anastrozole. Anastrozole is not appropriate therapy for premenopausal women.

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**BINV-E**

## ADJUVANT CHEMOTHERAPY 1,2,3

## Node negative

- **CMF**  
(cyclophosphamide/methotrexate/fluorouracil)
- **FAC/CAF**  
(fluorouracil/doxorubicin/cyclophosphamide)
- **AC** (doxorubicin/cyclophosphamide)

Node positive<sup>4</sup>

- **FAC/CAF**  
(fluorouracil/doxorubicin/cyclophosphamide)  
or  
**CEF**  
(cyclophosphamide/epirubicin/fluorouracil)
- **AC** (doxorubicin/cyclophosphamide) ±  
sequential paclitaxel<sup>5</sup>
- **A → CMF<sup>6</sup>** (doxorubicin followed by  
cyclophosphamide/methotrexate/fluorouracil)
- **CMF**  
(cyclophosphamide/methotrexate/fluorouracil)
- **EC** (epirubicin/cyclophosphamide)

<sup>1</sup>Retrospective evidence suggests that doxorubicin-based chemotherapy regimens may be superior to non-doxorubicin-based regimens in patients with tumors over-expressing HER-2 by IHC (category 2B).

<sup>2</sup>Trastuzumab should be used as adjuvant therapy only in the setting of a clinical trial.

<sup>3</sup>CMF and radiation therapy may be given concurrently, or the CMF may be given first. All other chemotherapy regimens should be given prior to radiotherapy.

<sup>4</sup>For node-positive patients, anthracycline-containing chemotherapy regimens are preferred.

<sup>5</sup>Early evidence suggests that AC followed by paclitaxel may be superior to AC alone in patients with hormone receptor negative tumors. The committee believes that more mature data are necessary before definitive recommendations can be made.

<sup>6</sup>The data supporting A → CMF are limited to patients with four or more positive nodes.

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**BINV-F**

## SUBSEQUENT HORMONAL THERAPY

### PREMENOPAUSAL PATIENTS

- Luteinizing hormone-releasing hormone agonists ± antiestrogen
- Surgical or radiotherapeutic oophorectomy
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol

### POSTMENOPAUSAL PATIENTS

- Selective aromatase inhibitor (anastrozole, letrozole) or aromatase inactivator (exemestane)
- Tamoxifen or Toremifene
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol

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**BINV-G**

## PREFERRED CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

### Preferred first-line chemotherapy:

**Anthracycline-based, taxane, or CMF**

### Preferred second-line chemotherapy:

**If first-line was anthracycline-based or CMF, then taxane**

**If first-line was taxane, then anthracycline-based or CMF**

**Other active agents include capecitabine, vinorelbine, gemcitabine, mitoxantrone, and platinum compounds**

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

**BINV-H**

## Staging

**Table 1**

### American Joint Committee on Cancer (AJCC) TNM Staging System For Breast Cancer

#### Primary Tumor (T)

- TX** Primary tumor cannot be assessed
- T0** No evidence of primary tumor
- Tis** Carcinoma *in situ*: Intraductal carcinoma, lobular carcinoma *in situ*, or Paget's disease of the nipple with no tumor.
- T1** Tumor 2 cm or less in greatest dimension
- T1mic** Microinvasion 0.1 cm or less in greatest dimension
- T1a** Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
- T1b** Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
- T1c** Tumor more than 1 cm but not more 2 cm in greatest dimension
- T2** Tumor more than 2 cm but not more than 5 cm in greatest dimension
- T3** Tumor more than 5 cm in greatest dimension
- T4** Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below
- T4a** Extension to chest wall
- T4b** Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
- T4c** Both (T4a and T4b)
- T4d** Inflammatory carcinoma (see definition of inflammatory carcinoma)

*Note:* Paget's disease associated with a tumor is classified according to the size of the tumor.

#### Regional Lymph Nodes (N)

- NX** Regional lymph nodes cannot be assessed (e.g., previously removed)
- N0** No regional lymph node metastasis
- N1** Metastasis to movable ipsilateral axillary lymph node(s)
- N2** Metastasis to ipsilateral axillary lymph node(s) fixed to one another or to other structures
- N3** Metastasis to ipsilateral internal mammary lymph node(s)

#### Pathologic Classification

- pNX** Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
- pN0** No regional lymph node metastasis
- pN1** Metastasis to movable ipsilateral axillary lymph node(s)
- pN1a** Only micrometastasis (none larger than 0.2 cm)
- pN1b** Metastasis to lymph node(s), any larger than 0.2 cm
- pN1bi** Metastasis in 1 to 3 lymph nodes, any more than 0.2 cm and all less than 2 cm in the greatest dimension
- pN1bii** Metastasis to 4 or more lymph nodes, any more than 0.2 cm and all less than 2 cm in greatest dimension
- pN1biii** Extension of tumor beyond the capsule of a lymph node metastasis less than 2 cm in greatest dimension
- pN1biv** Metastasis to a lymph node 2 cm or more in greatest dimension
- pN2** Metastasis to ipsilateral axillary lymph nodes that are fixed to one another or to other structures
- pN3** Metastasis to ipsilateral internal mammary lymph node(s)

*Continued*

**Table 1 (continued)**

**Distant Metastasis (M)**

- MX** Distant metastasis cannot be assessed
- M0** No distant metastasis
- M1** Distant metastasis (includes metastasis to ipsilateral supraclavicular lymph node[s])

Used with the permission of the American Joint Committee on Cancer (AJCC®) Chicago, Illinois. The original source for this material is the AJCC® Cancer Staging Manual, 5<sup>th</sup> edition (1997) published by Lippincott-Raven Publishers, Philadelphia.

**Stage Grouping**

<b>Stage 0</b>	Tis	N0	M0
<b>Stage I</b>	T1*	N0	M0
<b>Stage IIA</b>	T0	N1	M0
	T1*	N1**	M0
	T2	N0	M0
<b>Stage IIB</b>	T2	N1	M0
	T3	N0	M0
<b>Stage IIIA</b>	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
<b>Stage IIIB</b>	T4	Any N	M0
	Any T	N3	M0
<b>Stage IV</b>	Any T	Any N	M1

\*Note: T1 includes T1mic

\*\*Note: The prognosis of patients with N1a is similar to that of patients with pN0.

## Manuscript

### NCCN Categories of Consensus

**Category 1:** There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

**Category 2A:** There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

**Category 2B:** There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

**Category 3:** There is major NCCN disagreement that the recommendation is appropriate.

**All recommendations are category 2A unless otherwise noted.**

## Overview

The American Cancer Society estimates approximately 193,700 new cases of breast cancer will be diagnosed in the year 2001 and approximately 40,600 patients will die of this disease (Greenlee et al., 2001). Breast cancer is the most common malignancy in women in the United States and is second only to lung cancer as a cause of cancer death.

The incidence of breast cancer has increased steadily in the United States over the past few decades, while mortality has remained relatively constant, suggesting increased success from treatment. Over the past few years, breast cancer mortality appears to be declining among white women but increasing among black women (Smigel, 1995).

The etiology of the vast majority of breast cancer cases is unknown. However, a number of risk factors for the disease have been established. These risk factors include female gender, increasing age, family history of breast cancer at a young age, early menarche, late menopause, older age at first live childbirth, prolonged hormone replacement therapy, prior exposure to therapeutic irradiation, benign proliferative breast disease, and mutations in the genes BRCA1 and BRCA2. Except for female gender and increasing age, these risk factors are associated with only a minority of breast cancers. Women with a strong family history of breast cancer should be evaluated according to the NCCN Genetics/Family Screening Guideline. Women at increased risk for breast cancer (generally those with a greater than 1.67% 5-year risk of breast cancer) may consider risk reduction strategies (see NCCN Breast Cancer Risk Reduction Guideline).

Proliferative abnormalities of the breast are limited to the lobular and ductal epithelium. In both the lobular and ductal epithelium, a spectrum of proliferative abnormalities may be observed. These include hyperplasia, atypical hyperplasia, in situ carcinoma, and invasive carcinoma. Approximately 85% to 90% of invasive carcinomas are ductal in origin. The invasive ductal carcinomas include unusual variants of breast cancer (colloid or mucinous, adenoid cystic, tubular, and typical medullary carcinomas) which have especially favorable natural histories.

## Staging

The American Joint Committee on Cancer (AJCC) staging system for breast cancer is based on the TNM system ([Table 1](#)) (Fleming et al., 1997). Although the anatomically based AJCC staging system predicts survival, biological factors are also prognostic for survival and predictive of response to treatment. These biological factors

include age or menopausal status, number of involved axillary lymph nodes, presence or absence of estrogen and progesterone receptors, and HER2/*neu* expression. Within stage I, II and IIIA breast cancer, the biological factors, especially axillary lymph node status, provide more accurate prognostic information than does the TNM or AJCC stage.

### Treatment Approach

Conceptually, the treatment of breast cancer (except lobular carcinoma *in situ* [LCIS]) includes the treatment of local disease with surgery and/or radiation therapy and the treatment of systemic disease with cytotoxic chemotherapy and/or hormonal therapy. The need for, and selection of, various local or systemic therapies are based on a number of prognostic and predictive factors including tumor histology, clinical and pathologic characteristics of the primary tumor, axillary node status, tumor hormone receptor content, level of HER2/*neu* expression, presence or absence of detectable metastatic disease, comorbidity, and patient age.

In terms of treatment, breast cancer may be divided into (1) the pure non-invasive carcinomas, which include ductal carcinoma *in situ* (DCIS) and LCIS (stage 0); (2) operable, locoregional invasive carcinoma (stage I, stage II and some stage IIIA tumors); (3) inoperable locoregional invasive carcinoma (stage IIIB and some stage IIIA tumors); and (4) metastatic or recurrent carcinoma (stage IV).

The breast cancer guidelines presented here are the work of the members of the NCCN Breast Cancer Practice Guidelines Panel. Categories of evidence were assessed and are noted in the text. Although not explicitly stated at every decision point of the guidelines, patient participation in prospective clinical trials is the preferred option for all stages of breast cancer.

### Pure Noninvasive Carcinomas (Stage 0)

Both LCIS and DCIS may be difficult to distinguish from atypical hyperplasia or from carcinomas with early invasion (Rosai, 1991; Schnitt et al., 1992). Therefore, pathology review of all cases is appropriate. Bilateral diagnostic mammography should also be performed to identify the presence of multiple primary tumors and to estimate the extent of the noninvasive lesion.

Treatment of *in situ* carcinomas is aimed at either preventing the occurrence of invasive disease or diagnosing the invasive component when still localized to the breast. Patients found to have invasive disease on pathology review or at the time of reexcision or mastectomy should be treated according to the stage-appropriate guidelines for invasive carcinoma.

### Lobular Carcinoma *In Situ*

The preferred treatment of LCIS is observation alone. Consideration of bilateral mastectomy, with or without reconstruction, is a treatment option in special circumstances. Observation alone is the preferred option for women diagnosed with LCIS because their risk of developing invasive carcinoma is low (approximately 21% over 15 years) (Haagensen et al., 1981), the histologies of the invasive carcinomas tend to be favorable, and deaths from these second invasive cancers are unusual in appropriately observed women (Bradley et al., 1990).

The risk of an invasive breast cancer following a diagnosis of LCIS is equal in both breasts. Therefore, bilateral mastectomy is required to minimize risk absolutely. Women treated with bilateral mastectomy are appropriate candidates for breast reconstruction.

Women with LCIS, whether they are observed only or are treated with bilateral mastectomy, have an excellent prognosis. Recent data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial demonstrate tamoxifen, when given for 5 years, is associated with an approximate 56% reduction in the risk of developing invasive breast cancer among women with a history of LCIS (Fisher et al., 1998b). Thus, the use of tamoxifen should be considered in women with LCIS who are treated with observation. (For recommendations on risk-reduction, see the NCCN Breast Cancer Risk-Reduction Guidelines.)

Follow-up of patients with LCIS includes the performance of physical examinations every 6 to 12 months for 5 years and then annually. Also, in those being managed with observation, yearly mammography is recommended.

### Ductal Carcinoma In Situ

Patients with DCIS and evidence of widespread disease (two or more quadrants) by mammography, physical examination or biopsy require a total mastectomy without lymph node dissection. For the vast majority of patients with more limited disease in whom negative margins are achieved by the initial excision or by re-excision(s), breast conserving therapy or a total mastectomy are appropriate treatment options. Contraindications to breast conserving therapy requiring radiotherapy are listed on BINV-C. Prospective randomized trials have demonstrated that the addition of breast irradiation to a margin free excision of pure DCIS decreases rates of in-breast recurrence, but without difference in overall survival (Fisher et al., 1998c; Julien et al., 2000). However, there is considerable non-controlled evidence that selective omission of post-excision radiation does not affect survival, and that selected patients have a low risk of local failure with excision alone without

breast irradiation (Silverstein et al., 1996; Silverstein et al., 1999). Based upon high-level evidence from the randomized trials, the NCCN Guideline calls for the use of irradiation following excision alone in all patients with DCIS 0.5 cm or greater in diameter. It should be noted the definition of a negative margin has not been firmly established in this disease. There appears to be a consensus that margins >10 mm are negative and margins <1 mm are inadequate, but no uniform consensus exists for margin status between these values.

Axillary dissection is not recommended for patients with pure DCIS. Although mastectomy provides maximum local control, the long-term cause-specific survival with mastectomy versus excision and irradiation appears to be equivalent (Fisher et al., 1998c; Julien et al., 2000). Women treated with mastectomy are appropriate candidates for breast reconstruction.

Limited evidence suggests very small (less than 0.5 cm), unicentric, low-grade DCIS of the solid, cribriform or papillary subtypes may be managed with any of the following options: (1) excision plus radiotherapy; (2) total mastectomy, with or without reconstruction, and without lymph node dissection; or (3) excision alone followed by observation. A number of prospective studies are now underway evaluating the pathologic classification systems and treatment options for DCIS. The results of these studies will suggest modifications to the current guidelines.

Patients who receive breast conservation therapy should undergo post excision mammography of the involved breast and/or specimen radiography to ensure all mammographically detectable disease has been excised. Alternatively, specimen radiographs clearly documenting the abnormality (mass and microcalcifications) is clearly within the specimen are felt to be adequate documentation of

complete excision by some (Category 3). The Category 3 nature of this recommendation arises from disagreement whether or not specimen radiographs interpreted as demonstrating removal of all microcalcifications and/or masses are adequate documentation of complete excision.

Pathologically, DCIS falls between atypical ductal hyperplasia and invasive ductal carcinoma within the spectrum of proliferative abnormalities. The NSABP Breast Cancer Prevention Trial demonstrated an 86% reduction in the occurrence of invasive breast cancer in patients with atypical ductal hyperplasia who were treated with tamoxifen (Fisher et al., 1998b). The Early Breast Cancer Trialists' overview analysis showed, with 5 years of tamoxifen therapy, women with estrogen receptor positive or receptor unknown tumors had a 47% reduction in the annual odds of recurrence of invasive breast cancer (Early Breast Cancer Trialists' Collaborative Group, 1998b). Similarly, the NSABP B-24 trial found a benefit from tamoxifen in women with DCIS after treatment with breast conservation surgery and radiotherapy. This study randomized women with DCIS who were treated with breast-conserving therapy to placebo or tamoxifen. The women treated with tamoxifen had a 5% absolute reduction in risk and a 37% reduction in relative risk. The women receiving tamoxifen had an 8.2% total incidence of breast cancer (4.1% invasive and 4.2% noninvasive) compared to a 13.4% incidence of breast cancer (7.2% invasive and 6.2% noninvasive) in the placebo treated group (Fisher et al., 1999).

Tamoxifen treatment may, therefore, be considered in women with DCIS treated with breast-conserving therapy (category 1 for those undergoing BSC+RT; category 2A for those undergoing excision alone) and in women with DCIS treated with mastectomy (category 2B). The goal of such therapy is to decrease the development of a

contralateral, second primary, breast cancer (risk reduction therapy) or, in those who received breast-conserving therapy, to reduce the risk of an ipsilateral recurrence (adjuvant therapy).

Follow-up of women with DCIS includes a physical examination performed every 6 months for 5 years and then annually, as well as yearly mammography.

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

The recommended work-up and staging of invasive breast cancer includes a complete blood cell count, platelet count, liver function tests, chest radiograph, bilateral mammography, and, if necessary, breast ultra-sonography, tumor estrogen and progesterone receptor determinations, level of HER2/*neu* expression, and pathology review. Evaluation by magnetic resonance imaging (MRI) using a dedicated breast coil is considered optional, if available.

The determination of level of HER2/*neu* expression for all newly diagnosed patients with invasive breast cancer is a now recommended. HER2/*neu* level of expression is variably used to provide prognostic information, to predict for the superiority of anthracycline-based adjuvant chemotherapy over CMF chemotherapy, and to predict for benefit from trastuzumab therapy in women with recurrent or metastatic breast cancer. Only the use of HER2/*neu* expression to predict for trastuzumab sensitivity has been prospectively studied. HER2/*neu* expression has been assessed by measuring the number of gene copies (fluorescence in situ hybridization; FISH), the number of cell surface oncoproteins (immunohistochemistry; IHC) or by level of circulating receptor protein. Multiple different methodologies have been utilized to perform these determinations, but few have FDA approval: the IHC

HercepTest (DAKO, Glostrup, Denmark) which is approved for predicting responsiveness to trastuzumab, the INFORM HER-2/*neu* (Oncor, Inc.) FISH test for assigning prognosis, and the PathVysion HER-2 DNA Probe Kit (Vysis, inc.) FISH test for prognosis and for predicting anthracycline sensitivity. The requirement for determination of HER2/*neu* expression in the initial work-up is for prognostic purposes in patients with node negative breast cancer (Category 2B) (Cooke et al., 2001), to assist in the selection of adjuvant therapy where retrospective data suggests that doxorubicin-based adjuvant therapy may be superior to non-doxorubicin-based chemotherapy in patients with tumors over-expressing HER2/*neu* (Category 2B) (Paik et al., 1998; Paik et al., 2000; Piccart et al., 2000; Thor et al., 1998), and as baseline information to be considered should the individual develop recurrent disease requiring consideration for trastuzumab therapy (Category 1) (Cobleigh et al., 1999; Slamon et al., 2001; Vogel et al., 2001). The relative role of IHC versus FISH testing for HER2/*neu* expression/amplification in providing prognostic or predictive information has not yet been fully defined (Field et al., 2001; Lebeau et al., 2001; Tubbs et al., 2001; Wang et al., 2000). However, early data suggests that amplified HER2/*neu* by FISH analysis is a better predictor of trastuzumab responsiveness than IHC for those patients with HER2/*neu* expression of 2+ by the HercepTest.

The guidelines designate the performance of a bone scan as optional, except in the presence of localized symptoms or elevation of alkaline phosphatase, in which case a bone scan is required.

Interpreting the results of staging studies and assigning clinical stage are a dynamic process. Additional studies, such as computed tomography (CT), ultrasound or MRI of the liver in patients with abnormal liver function, may be required to further evaluate

abnormalities in the initial staging studies or if pathologic staging reveals high-risk disease, i.e. 4 or more positive nodes.

### Locoregional Treatment

A number of randomized trials document, in the majority of women with stage I and stage II breast cancers, mastectomy with axillary lymph node dissection or breast-conserving therapy with lumpectomy, axillary dissection and breast irradiation are medically equivalent primary treatment options (category 1) (Arriagada et al., 1996; Early Breast Cancer Trialists' Collaborative Group, 1995; Fisher et al., 1995; Veronesi et al., 1995). If adjuvant chemotherapy is indicated, the radiation therapy should be given following the completion of the chemotherapy. Breast conserving radiation therapy may be given concurrent with CMF chemotherapy, but methotrexate should either be withheld during the radiation or limited to no more than 2 doses concurrent with the radiation. The impact of concurrent CMF chemotherapy with radiation therapy has been demonstrated to decrease the cosmetic outcome of breast conserving therapy in some, but not all studies (Abner et al., 1991; Dubey et al., 1999; Markiewicz et al., 1996).

Radiotherapy (RT) is absolutely contraindicated during pregnancy, if the patient has had previous RT to the breast or chest wall, for diffuse suspicious or malignant appearing microcalcifications on mammography, and for multicentric disease (disease involving 2 or more quadrants of the breast).

Relative contraindications to breast-conserving therapy include multifocal disease requiring two or more separate surgical excisions, preexisting connective tissue disease other than rheumatoid arthritis (especially scleroderma) and tumors >5 cm (Category 2B).

A typical woman with clinical stage I or stage II breast cancer requires pathologic assessment of the axillary lymph node status. Traditionally, pathologic assessment of axillary lymph nodes has required the performance of a formal level I and level II axillary dissection. The axillary dissection should be extended to include level III nodes only if gross disease is apparent in the level I or level II nodes.

The current guidelines are modified from the earlier version to include a guideline for Surgical Axillary Staging for Stage I, IIA, and IIB breast cancer (BINV-A). This allows for the performance of a sentinel lymph node biopsy (category 2B) in certain circumstances to assess the pathologic status of the axillary lymph nodes (Bass et al., 1999; Cox, 2001; Cox et al., 2001; Krag et al., 1998; McMasters et al., 1998; O'Hea et al., 1998; Veronesi et al., 1997). Not all women are candidates for sentinel lymph node biopsy. Appropriate candidates are those for whom an experienced sentinel lymph node team is available (Dupont et al., 2001). In addition, potential candidates should have clinically negative axillary lymph nodes, a primary tumor <5 cm in greatest diameter, no large prior excision (>6 cm), and no preoperative chemotherapy or hormonal therapy. If the sentinel lymph node cannot be identified or is found to be positive for metastasis, a formal axillary lymph node dissection should be performed. If lymph node mapping identifies sentinel lymph nodes in the internal mammary chain, internal mammary node excision is considered optional (Category 3). In many institutions, sentinel lymph nodes are assessed for the presence of metastasis by both hematoxylin and eosin staining and by cytokeratin immunohistochemistry. The significance of a lymph node that is negative by hematoxylin and eosin staining but positive by cytokeratin immunohistochemistry is controversial. As the historical

and clinical trial data upon which treatment decisions are based have relied upon hematoxylin and eosin staining, the panel believes that treatment decisions should currently be made based solely upon hematoxylin and eosin staining (Category 3). In the uncommon situation where the hematoxylin and eosin staining is equivocal, reliance upon the results of cytokeratin immunohistochemistry is reasonable.

*It should be emphasized that the performance of a level I and II axillary dissection is an appropriate staging study in women with invasive breast cancer. Thus, sentinel lymph node mapping and excision should be considered an option to axillary lymph node dissection in selected patients, but not a mandatory replacement for a level I and II axillary dissection.*

Furthermore, in the absence of definitive data demonstrating superior survival from the performance of axillary lymph node dissection, the performance of axillary lymph node dissection may be considered optional in patients who have particularly favorable tumors, those for whom the selection of adjuvant systemic therapy is unlikely to be affected, the elderly, and those with serious comorbid conditions.

Women who undergo mastectomy are appropriate candidates for breast reconstruction.

### **Preoperative Chemotherapy for Large Stage IIA and IIB Tumors**

Women with large stage IIA and stage IIB tumors meeting the criteria for breast-conserving therapy except for size should be considered for preoperative chemotherapy. In some patients, anthracycline-based chemotherapy given before surgery resulting in sufficient tumor response may make breast conservation therapy possible. The results

of the NSABP B-18 trial show breast conservation rates are higher after preoperative chemotherapy (Fisher et al., 1998a). It should be noted, however, preoperative chemotherapy has failed to demonstrate a survival advantage over post-operative adjuvant chemotherapy in patients with stage II tumors.

If the tumor responds to chemotherapy, lumpectomy plus axillary lymph node dissection may be considered if the patient fills the requirement for breast-conserving therapy. Breast-conserving surgery should be followed by individualized chemotherapy such as taxanes (category 2B) and breast and regional lymph node irradiation. If, after 3-4 cycles of preoperative chemotherapy, the tumor fails to respond or the response is minimal or if there is progression at any point, a mastectomy plus axillary dissection, with or without breast reconstruction, should be performed. Adjuvant treatment for these patients consists of individualized chemotherapy followed by radiation therapy to the chest wall and supraclavicular nodes. After radiation therapy, all patients with estrogen receptor positive tumors should receive tamoxifen.

### **Radiation Therapy after Mastectomy**

Patients treated with total mastectomy whose tumors are more than 5 cm in greatest diameter or have positive surgical margins are at sufficiently high risk for local recurrence to warrant the use of postmastectomy radiotherapy to the chest wall as well as the supraclavicular nodes if indicated.

Three randomized trials have demonstrated a disease-free and overall survival advantage conferred by the addition of chest wall and regional lymph node irradiation in women with positive axillary lymph nodes following mastectomy and axillary lymph node dissection (Hellman, 1997; Overgaard et al., 1997; Overgaard et

al., 1999; Ragaz et al., 1997; Recht et al., 2001). In these trials, not only the ipsilateral chest wall but also the ipsilateral locoregional lymph nodes were irradiated. These studies contrast, however, with a number of other studies, including one randomized trial from an NCCN institution (Theriault et al., 1998), which fail to demonstrate a survival advantage with postmastectomy chest wall and regional node irradiation. On the basis of these recent studies suggesting a survival advantage with postmastectomy chest wall and regional lymph node irradiation in node positive breast cancer, the current guidelines call for the consideration of postmastectomy irradiation in such women.

For women with one to three involved axillary lymph nodes, the guidelines now state irradiation to the chest wall and supraclavicular area should be considered following chemotherapy. This is listed as a category 1 recommendation with a footnote documenting the contradictory data regarding survival benefit related to this subset of patients. It should also be noted that the risk of local recurrence is low in the absence of radiation therapy. This recommendation generated substantial controversy among the panel. Some of the panel members believe irradiation should be used routinely, other members believe irradiation should not be mandatory, given the other available studies which fail to demonstrate an advantage.

Furthermore, there was considerable disagreement (category 3) regarding the inclusion of the ipsilateral internal mammary field. Some panel members felt irradiation of the internal mammary nodes was unnecessary and produced too much morbidity. Others felt the internal mammary field should be included, as it was in the studies which demonstrated an advantage to postmastectomy, postchemotherapy radiation.

Women with four or more positive axillary lymph nodes are also at increased risk for local recurrence. The use of routine, postmastectomy, postchemotherapy chest wall and regional lymph node irradiation is recommended (category 1). The use of prophylactic chest wall radiotherapy in this setting substantially reduces the risk of local recurrence (Early Breast Cancer Trialists' Collaborative Group, 1995). Again, there was substantial disagreement among panel members regarding the inclusion of the ipsilateral internal mammary field (category 3).

Radiation is not recommended for patients with negative margins, tumors 5 cm or smaller, and no positive axillary lymph nodes.

### Systemic Adjuvant Therapy

After local surgical treatment, adjuvant systemic therapy should be considered. The recent updates of the Early Breast Cancer Trialists' Collaborative Group overview analyses of adjuvant polychemotherapy and tamoxifen now demonstrate convincing reductions in the odds of recurrence and of death in all age groups under 70 years of age (Early Breast Cancer Trialists' Collaborative Group, 1998a; Early Breast Cancer Trialists' Collaborative Group, 1998b). Thus, the current guidelines recommend adjuvant therapy without regard to patient age. The decision to utilize systemic adjuvant therapy requires the consideration and balancing of risk for recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, the toxicity of the therapy, and comorbidity (Loprinzi and Thome, 2001). The decision making process requires a collaborative decision making process involving the health care provider and patient.

The NCCN Guidelines call for the determination of estrogen and progesterone receptor content on all primary invasive breast

cancers. Patients with invasive breast cancers that are estrogen and/or progesterone receptor positive should be considered for adjuvant hormonal therapy regardless of age, lymph node status or whether or not adjuvant chemotherapy is to be administered (Early Breast Cancer Trialists' Collaborative Group, 1998b). Selected studies suggest breast cancers that overexpress the *HER2/neu* oncogene may be relatively hormone refractory, although other studies have failed to confirm this finding (Berry et al., 2000; Eppenberger-Castori et al., 2001; Knoop et al., 2001; Mass, 2000; Pegram et al., 1998; Piccart et al., 2000). However, given the inconsistency of these data and the favorable toxicity profile of the available hormonal therapies, the Panel continues to recommend the use of tamoxifen as adjuvant therapy in women with hormone receptor positive breast cancer regardless of menopausal status, age, or *HER2/neu* status (See [Table 2](#)), with the exception of those with lymph node negative cancers  $\leq 0.5$  cm or 0.6 to 1.0 cm in diameter and with favorable prognostic features.

Small tumors up to 0.5 cm in greatest diameter, which do not involve the lymph nodes, are so favorable; that adjuvant systemic therapy is of minimal incremental benefit and is not recommended. Patients with invasive ductal or lobular tumors 0.6 to 1 cm in diameter and no lymph node involvement may be divided into those with a low risk of recurrence and those with unfavorable prognostic features which warrant consideration of adjuvant therapy. Unfavorable prognostic features include angiolymphatic invasion, high nuclear grade, high histologic grade, *HER-2* overexpression, or hormone receptor negative (category 2B).

The guidelines also provide systemic treatment recommendations for the favorable-histology invasive breast cancers, i.e., tubular, colloid and typical medullary, based on tumor size. The pathologic

classification of typical medullary carcinoma is pathologically challenging and of substantial clinical importance. Carcinomas fulfilling some, but not all of the features of medullary carcinoma are often biologically aggressive, while typically medullary breast cancers have a favorable natural history (Jensen et al., 1997). There is evidence that medullary breast cancer is over-diagnosed, and the Panel specifically recommends the classification system for medullary breast cancer of Ridolfi (Pedersen et al., 1991; Ridolfi et al., 1977).

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, greater than 1 cm in diameter, chemotherapy is recommended (category 1). For those with lymph node negative, hormone receptor positive tumors, greater than 1 cm but not more than 3 cm in diameter, tamoxifen with chemotherapy is recommended (category 1). The use of chemotherapy or tamoxifen in these subsets of patients must be based on balancing the absolute magnitude of risk reduction expected and the individual patient's willingness to experience toxicity in order to achieve incremental risk reduction.

Patients with lymph node positive disease are candidates for chemotherapy and, if also hormone receptor positive, for the addition of tamoxifen (category 1). The paucity of clinical trial data regarding adjuvant chemotherapy in women over the age of 70 years prohibits definitive recommendations in this age group. Adjuvant treatment in women over 70 years should be individualized with consideration of comorbid conditions.

For axillary lymph node negative breast cancer, appropriate regimens include cyclophosphamide, methotrexate and 5-

fluorouracil (CMF); fluorouracil, doxorubicin and cyclophosphamide (FAC/CAF); or doxorubicin and cyclophosphamide (AC). In women with node positive disease, FAC/CAF or cyclophosphamide, epirubicin and fluorouracil (CEF); AC alone; AC followed by paclitaxel; doxorubicin followed by CMF; or CMF alone, or epirubicin and cyclophosphamide (EC) are all considered to be appropriate options.

Studies of CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy versus no chemotherapy have demonstrated disease free and overall survival advantage with CMF chemotherapy (Early Breast Cancer Trialists' Collaborative Group, 1998a). Studies using CAF/FAC (cyclophosphamide, doxorubicin, 5-fluorouracil) chemotherapy have demonstrated that the use of full dose chemotherapy regimens is important (Wood et al., 1994). In the Early Breast Cancer Trialists' overview of polychemotherapy, comparison of anthracycline-containing regimens to CMF demonstrated 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 (Early Breast Cancer Trialists' Collaborative Group, 1998a). Based on these data, the panel qualified the appropriate chemotherapy regimens by the statement, for node positive patients, anthracycline-containing regimens are preferred. This analysis, however, did not consider the potential interaction of level of HER2/*neu* expression and efficacy of anthracycline containing versus CMF chemotherapy regimens. Retrospective analysis has suggested that the superiority of anthracycline containing chemotherapy may be limited to the treatment of those breast cancers that overexpress the HER2/*neu* oncogene (Mass, 2000; Menard et al., 2001; Muss et al., 1994; Paik et al., 2000; Thor et al., 1998). This retrospective finding across several clinical trials that doxorubicin-based chemotherapy may be

more efficacious in patients whose tumors overexpress HER2/*neu* (Paik et al., 1998; Paik et al., 2000; Thor et al., 1998) has led to a footnote noting doxorubicin-based chemotherapy may be superior to non-doxorubicin-containing regimens in the adjuvant treatment of such patients (category 2B).

AC chemotherapy (cyclophosphamide and doxorubicin) has been studied in randomized trials, resulting in relapse-free and overall survival equivalent to CMF chemotherapy (Bang et al., 2000; Fisher et al., 2001; Fisher et al., 1990). There is no demonstrated benefit from dose intensification of either doxorubicin or cyclophosphamide in the published AC series (Fisher et al., 1997; Henderson et al., 1998). A single study in women with 4 or more involved axillary lymph nodes compared the use of sequential versus alternating doxorubicin and CMF chemotherapy and found the sequential regimen superior (Bonadonna et al., 1995; Silvestrini et al., 2000).

The early results of a randomized trial comparing AC chemotherapy with or without sequential paclitaxel chemotherapy in women with axillary node positive breast cancer suggests improved disease free and overall survival with the addition of paclitaxel (Henderson et al., 1998). On retrospective analysis, the apparent advantage of the paclitaxel-containing regimen appears limited primarily to those women with estrogen-receptor negative breast cancers. The mature results of both this trial and a trial of similar design from the National Surgical Adjuvant Breast and Bowel Project (NSABP B-28) are required before definitive recommendations can be made.

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 classic CMF chemotherapy versus CEF

chemotherapy utilizing high dose epirubicin. Five-year relapse free survival (63% vs. 53%;  $p=0.009$ ) and overall survival (77% vs. 70%;  $p=0.03$ ) both favored the CEF arm of the trial (Levine et al., 1998). The second trial compared CEF given all IV every three weeks two dose levels of epirubicin ( $50 \text{ mg/m}^2$  vs.  $100 \text{ mg/m}^2$ ) in premenopausal and postmenopausal women with node positive breast cancer. Five-year disease free survival (55% vs 66%;  $p=0.03$ ) and overall survival (65% vs 76%;  $p=0.007$ ) both favored the epirubicin  $100 \text{ mg/m}^2$  arm (French Adjuvant Study Group, 2001). A recent trial compared two dose levels of EC chemotherapy with CMF chemotherapy in woman with node-positive breast cancer (Piccart et al., 2001). This study demonstrated that higher dose EC chemotherapy was equivalent to CMF chemotherapy and superior to moderate dose EC in event free survival and overall survival.

The guidelines include a footnote stating women younger than 50 years of age with functioning ovaries and lymph node negative or lymph node positive, hormone receptor positive, invasive breast cancer experience reductions in the risk of recurrence and death from the use of radiation or surgical ovarian ablation or chemical suppression of the ovaries equivalent to the risk reductions achieved with polychemotherapy (Boccardo et al., 2000; Group, 1996). Therefore, surgical or radiation ablation or chemical suppression of the ovaries may be considered an option in these women.

### Stage IIIA or IIIB Invasive Breast Cancer

The staging evaluation for patients with stage IIIA or stage IIIB invasive breast cancer is similar to the one for patients with stage I or stage II disease. The guidelines include a bone scan (category

2B) and an abdominal CT, ultrasound, or MRI scan (category 2B), even in the absence of symptoms or liver enzyme abnormalities.

### **Operable Stage IIIA (T3, N1, M0) Breast Cancer**

Stage IIIA patients are divided into those who have T3, N1, M0 disease versus those who have any T, N2, M0 disease, based on evaluation by a multidisciplinary team. For patients with T3, N1, M0 disease, treatment is as outlined in BINV-1 through BINV-6.

Post-surgical systemic adjuvant therapy for patients with stage IIIA breast cancer who do not receive neoadjuvant chemotherapy is similar to post-surgical systemic adjuvant therapy for patients with stage II disease.

### **Inoperable Stage IIIA (any T, N2, M0) or Stage IIIB Breast Cancer**

For patients with clinical stage IIIA disease whose disease is inoperable and those with clinical stage IIIB disease, the initial use of anthracycline-based preoperative chemotherapy is standard therapy (Hortobagyi et al., 2000). Local therapy following preoperative therapy consists of (1) total mastectomy with axillary lymph node dissection, with or without delayed breast reconstruction, or (2) lumpectomy and axillary dissection. Both local treatment groups are considered to have sufficient risk of local recurrence to warrant the use of chest wall (or breast) and supraclavicular node irradiation. With N3 tumors, the internal mammary lymph nodes should also be irradiated.

A third treatment option following preoperative chemotherapy high-dose breast and regional lymph node irradiation alone generated considerable disagreement among the panel (category 3). The recommendation was included, however, because limited experience at selected institutions suggests high-dose breast and

regional lymph node irradiation may provide long term local control equivalent to surgery plus breast and regional node irradiation (Favret et al., 2001).

Patients with an inoperable stage IIIA or stage IIIB tumor, whose disease progresses during preoperative therapy, should be considered for palliative breast irradiation in an attempt to enhance local control. In all subsets of patients, further systemic adjuvant chemotherapy following local therapy is felt to be standard. Tamoxifen should be added for those with hormone receptor positive tumors or those with unknown hormone receptor status.

The panel continues to believe the available data do not warrant the inclusion of high-dose therapy with rescue within the standard guidelines. The panel does believe patients with stage IIIB breast cancer are a subset of patients for whom disease-oriented clinical trials of high-dose therapy with rescue are especially appropriate. Post-treatment follow-up for women with stage IIIA and stage IIIB disease is the same as for women with earlier-stage, invasive breast cancer.

### **Surveillance/Follow-up**

Post-therapy follow-up is optimally performed by a member or members of the treatment team and includes the performance of regular physical examinations and mammography. In patients undergoing breast-conserving therapy, the first follow-up mammogram should be performed approximately 6 months following the completion of breast-conserving radiotherapy. The routine performance of alkaline phosphatase and liver function tests are not included in the guidelines (Rosselli Del Turco et al., 1994; Smith et al., 1999; The GIVIO Investigators, 1994)

In addition, the panel continues to believe determination of the available “tumor markers” for breast cancer and routine bone scans

in the asymptomatic patient provide no advantage in survival or ability to palliate recurrent disease and are, therefore, not recommended (Bast et al., 2001).

Because of the risk of tamoxifen-associated endometrial carcinoma, the panel does recommend women with an intact uterus who are taking tamoxifen have a yearly pelvic examination, coupled with rapid evaluation of vaginal spotting. The performance of endometrial biopsy or ultrasonography is not recommended. Neither test has demonstrated utility as a screening test in any population of women. The vast majority of women with tamoxifen-associated uterine carcinoma have early vaginal spotting.

#### Stage IV and Metastatic or Recurrent Breast Cancer

The guideline recommends a patient with Stage IV, any T, any N, M1 disease in which the only site of metastasis is an ipsilateral, supraclavicular lymph node should be treated as Stage IIIB disease (Category 2B) (Brito et al., 2001). All other Stage IV patients should be treated according to the algorithm for recurrent disease.

The staging evaluation of women who present with metastatic or recurrent breast cancer includes the performance of a CBC, platelet count, liver function tests, chest x-ray, bone scan, x-rays of long or weight-bearing bones or bones which appear abnormal on bone scan, consideration of CT or MRI scan of chest and abdomen, biopsy documentation of first recurrence if possible, and determination of HER-2 status by IHC and/or FISH.

#### Local Disease Only

Patients with local recurrence only are divided into those who had initially been treated by mastectomy and those who had received

breast-conserving therapy. Mastectomy-treated patients should undergo surgical resection of the local recurrence, if it can be accomplished without heroic surgery, and involved-field radiotherapy (if the chest wall was not previously treated or if additional radiotherapy may be safely administered). The use of surgical resection in this setting implies the use of limited excision of disease with the goal of obtaining clear margins of resection. Women whose disease recurs locally following initial breast-conserving therapy should undergo a total mastectomy.

Following local treatment, women with local recurrences should be considered for systemic chemotherapy or hormonal therapy, as is the case for those women with systemic recurrences.

#### Systemic Disease

The treatment of systemic recurrence of breast cancer prolongs survival and enhances quality of life but is not curative. Therefore, treatments associated with minimal toxicity are preferred. Thus, the use of the minimally toxic hormonal therapies is preferred to the use of cytotoxic therapy whenever reasonable.

Women with osteolytic lesions may be given pamidronate if expected survival is 3 months or greater and creatinine levels are below 2.5 mg/dL (category 1). Pamidronate may be given in addition to chemotherapy or hormonal therapy (Conte et al., 1996; Hortobagyi et al., 1998; Theriault et al., 1999).

Women considered to be appropriate candidates for initial hormonal therapy for treatment of recurrent or metastatic disease include those whose tumors are estrogen and/or progesterone positive, those with bone or soft tissue disease only, or those with limited, asymptomatic visceral disease.

In postmenopausal women with prior antiestrogen therapy and who are within one year of antiestrogen exposure, recent evidence supports the use of a selective, non-steroidal aromatase inhibitor such as anastrozole or letrozole as the preferred second-line therapy (Buzdar et al., 2001; Buzdar et al., 1998). For postmenopausal women who are antiestrogen naïve or who have not been exposed to antiestrogen therapy for greater than one year, the selective, non-steroidal aromatase inhibitors appear to have superior outcome compared with tamoxifen, although the differences are modest (Bonnetterre et al., 2000; Mouridsen et al., 2001; Nabholz et al., 2000; Vergote et al., 2000). Therefore, either tamoxifen or an aromatase inhibitor is an appropriate option.

In premenopausal women with prior antiestrogen therapy and who are within one year of antiestrogen exposure, the preferred second-line therapy is either surgical or radiotherapeutic oophorectomy or leutenizing hormone-releasing hormone agonists with or without an antiestrogen. In premenopausal women without prior exposure to an antiestrogen, initial treatment with an antiestrogen with or without a leutenizing hormone-releasing hormone agonist is preferred (Klijn et al., 2001).

Many pre- and postmenopausal women derive benefit from sequential hormonal therapy at the time of progression. Therefore, women whose breast cancers respond to a hormonal maneuver, with either shrinkage of the tumor or long-term stabilization of their disease, should receive additional hormonal therapy at the time of progression. Additional hormonal therapies for third and subsequent therapy are listed on BINV-F and in postmenopausal women, selective, steroidal aromatase inhibitors (exemestane); progestins (megestrol acetate); androgens (fluoxymesterone); high-

dose estrogen (ethinyl estradiol); and, in pre-menopausal women, luteinizing hormonereleasing hormone (LHRH) agonists and surgical or radiotherapeutic oophorectomy, progestins (megestrol acetate, androgens (fluoxymesterone); high-dose estrogen (ethinyl estradiol).

Women with estrogen and progesterone receptor negative tumors, symptomatic visceral metastasis, or hormone refractory disease should receive chemotherapy. A wide variety of chemotherapy regimens are felt to be appropriate, as outlined in BINV-G. Preferred first line chemotherapies include anthracycline-based combinations (e.g. AC, CAF/FAC), the taxanes (paclitaxel or docetaxel) or CMF. Preferred second-line therapies include cross-over to either a taxane or to anthracycline-based combinations or CMF. Other active agents for subsequent therapy include capecitabine, vinorelbine, gemcitabine, mitoxantrone, and platinum compounds. As with hormonal therapy, sequential responses with chemotherapy are often observed, and supports the use of sequential chemotherapy regimens.

Patients with tumors that overexpress *HER2/neu* may derive benefit from treatment with trastuzumab as a single agent or in combination with selected chemotherapeutic agents. The optimal method of selecting the subset of patients most likely to benefit from trastuzumab is rapidly evolving. When tested by the DAKO HercepTest, IHC staining of 2+ or 3+ appears to correlate with disease response to trastuzumab. However, benefit from trastuzumab treatment in patients with breast cancer IHC 2+ for *HER2/neu* appears to be limited to those tumors that are FISH positive for *HER2/neu* amplification. Therefore, the panel recommends selecting patients for trastuzumab who have tumors

either IHC 3+ for HER2/*neu* by the HercepTest or IHC 2+ for HER2/*neu* by the HercepTest and FISH amplified (Field et al., 2001; Tubbs et al., 2001; Wang et al., 2000). Patients with tumors IHC 0 or 1+ for HER2/*neu* have very low rates of trastuzumab response and therapy with trastuzumab is not warranted. In patients with metastatic or recurrent breast cancer whose tumors overexpress HER2/*neu*, trastuzumab as a single agent (Cobleigh et al., 1999; Vogel et al., 2001) or in combination with selected chemotherapeutics (Slamon et al., 2001) may be considered. A single randomized trial demonstrates benefit from adding trastuzumab to paclitaxel chemotherapy in patients with IHC 2+ or 3+ for HER2/*neu*. Early non-randomized data are available supporting the addition of agents such as docetaxel, vinorelbine, and platinum compounds in combination with trastuzumab. The panel believes the 27% frequency of significant cardiac dysfunction in patients treated with the combination of trastuzumab and doxorubicin/cyclophosphamide chemotherapy is too high for use of this combination outside the confines of a prospective clinical trial (Slamon et al., 2001).

Failure to achieve a tumor response to two sequential chemotherapy regimens or an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or greater was felt to be an indication for supportive therapy only (category 2B) or a clinical trial. 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 a number of anatomically localized problems which may benefit from local irradiation, surgery or regional chemotherapy (e.g., intrathecal methotrexate for leptomeningeal carcinomatosis).

### 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, ultimately, select the most appropriate option from among the available alternatives.

With rare exception, the evaluation, treatment and follow-up recommendations contained within these guidelines were based largely on the results of past and present clinical trials. However, there is not a single clinical situation in which the treatment of breast cancer has been optimized with respect to either maximizing cure or minimizing toxicity and disfigurement. Therefore, patient and physician participation in prospective clinical trials allows patients to not only receive state-of-the-art cancer treatment but also contribute to the improvement of treatment of future patients.

**Table 2****Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer****Preferred first-line chemotherapy:**

- Anthracycline-based
- Taxane<sup>a</sup>
- Cyclophosphamide, methotrexate, and 5-fluorouracil (CMF)

**Preferred second-line chemotherapy:**

- If first-line was anthracycline-based or CMF, then a taxane
- If first-line was a taxane, then anthracycline-based or CMF
- Other active regimens include capecitabine, 5-fluorouracil (via infusion), vinorelbine, and mitoxantron

<sup>a</sup> In patients whose tumors overexpress *HER2/neu*, consideration may be given to using trastuzumab in combination with paclitaxel. Trastuzumab has also been given in combination with doxorubicin and cyclophosphamide (AC), but the use of trastuzumab plus AC is associated with significant cardiac toxicity.

## References

Abner, A. L., A. Recht, F. A. Vicini, B. Silver, D. Hayes, S. Come, and J. R. Harris, Cosmetic results after surgery, chemotherapy, and radiation therapy for early breast cancer, *Int J Radiat Oncol Biol Phys*, 21, 331-338, 1991.

Arriagada, R., M. G. Le, F. Rochard, and G. Contesso, 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*, 14, 1558-1564, 1996.

Bang, S. M., D. S. Heo, K. H. Lee, J. H. Byun, H. M. Chang, D. Y. Noh, K. J. Choe, Y. J. Bang, S. R. Kim, and N. K. Kim, Adjuvant doxorubicin and cyclophosphamide versus cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy in premenopausal women with axillary lymph node positive breast carcinoma, *Cancer*, 89, 2521-2526, 2000.

Bass, S. S., G. H. Lyman, C. R. McCann, N. N. Ku, C. Berman, K. Durand, M. Bolano, S. Cox, C. Salud, D. S. Reintgen, and C. E. Cox, Lymphatic Mapping and Sentinel Lymph Node Biopsy, *Breast J*, 5, 288-295, 1999.

Bast, R. C., Jr, P. Ravdin, D. F. Hayes, S. Bates, H. Fritsche, Jr, J. M. Jessup, N. Kemeny, G. Y. Locker, R. G. Mennel, and M. R. Somerfield, 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*, 19, 1865-1878, 2001.

Berry, D. A., H. B. Muss, A. D. Thor, L. Dressler, E. T. Liu, G. Broadwater, D. R. Budman, I. C. Henderson, M. Barcos, D. Hayes,

and L. Norton, HER-2/neu and p53 expression versus tamoxifen resistance in estrogen receptor-positive, node-positive breast cancer, *J Clin Oncol*, 18, 3471-3479, 2000.

Boccardo, F., A. Rubagotti, D. Amoroso, M. Mesiti, D. Romeo, P. Sismondi, M. Gai, F. Genta, P. Pacini, V. Distanti, A. Bolognesi, D. Aldrighetti, and A. Farris, Cyclophosphamide, methotrexate, and fluorouracil versus tamoxifen plus ovarian suppression as adjuvant treatment of estrogen receptor-positive pre-/perimenopausal breast cancer patients: results of the Italian Breast Cancer Adjuvant Study Group 02 randomized trial. boccardo@hp380.ist.unige.it, *J Clin Oncol*, 18, 2718-2727, 2000.

Bonadonna, G., M. Zambetti, and P. Valagussa, Sequential or alternating doxorubicin and CMF regimens in breast cancer with more than three positive nodes. Ten-year results, *Jama*, 273, 542-547, 1995.

Bonneterre, J., B. Thurlimann, J. F. Robertson, M. Krzakowski, L. Mauriac, P. Koralewski, I. Vergote, A. Webster, M. Steinberg, and M. von Euler, 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*, 18, 3748-3757, 2000.

Bradley, S. J., D. W. Weaver, and D. L. Bouwman, Alternatives in the surgical management of in situ breast cancer. A meta-analysis of outcome, *Am Surg*, 56, 428-432, 1990.

Brito, R. A., V. Valero, A. U. Buzdar, D. J. Booser, F. Ames, E. Strom, M. Ross, R. L. Theriault, D. Frye, S.-W. Kau, L. Asmar, M. McNeese, S. E. Singletary, and G. N. Hortobagyi, Long-Term Results of Combined-Modality Therapy for Locally Advanced Breast Cancer

With Ipsilateral Supraclavicular Metastases: The University of Texas M.D. Anderson Cancer Center Experience, *J Clin Oncol*, 19, 628-633, 2001.

Buzdar, A., J. Douma, N. Davidson, R. Elledge, M. Morgan, R. Smith, L. Porter, J. Nabholz, X. Xiang, and C. Brady, Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate, *J Clin Oncol*, 19, 3357-3366, 2001.

Buzdar, A. U., W. Jonat, A. Howell, S. E. Jones, C. P. Blomqvist, C. L. Vogel, W. Eiermann, J. M. Wolter, M. Steinberg, A. Webster, and D. Lee, 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*, 83, 1142-1152, 1998.

Cobleigh, M. A., C. L. Vogel, D. Tripathy, N. J. Robert, S. Scholl, L. Fehrenbacher, J. M. Wolter, V. Paton, S. Shak, G. Lieberman, and D. J. Slamon, 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*, 17, 2639-, 1999.

Conte, P. F., J. Latreille, L. Mauriac, F. Calabresi, R. Santos, D. Campos, J. Bonnetterre, G. Francini, and J. M. Ford, 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*, 14, 2552-2559, 1996.

Cooke, T., J. Reeves, A. Lanigan, and P. Stanton, HER2 as a prognostic and predictive marker for breast cancer, *Ann Oncol*, 12 Suppl 1, S23-28, 2001.

Cox, C. E., Lymphatic mapping in breast cancer: combination technique, *Ann Surg Oncol*, 8, 67S-70S, 2001.

Cox, C. E., K. Nguyen, R. J. Gray, C. Salud, N. N. Ku, E. Dupont, L. Hutson, E. Peltz, G. Whitehead, D. Reintgen, and A. Cantor, Importance of lymphatic mapping in ductal carcinoma in situ (DCIS): why map DCIS?, *Am Surg*, 67, 513-519; discussion 519-521, 2001.

Dubey, A., A. Recht, S. E. Come, R. S. Gelman, B. Silver, J. R. Harris, and L. N. Shulman, Concurrent CMF and radiation therapy for early stage breast cancer: results of a pilot study, *Int J Radiat Oncol Biol Phys*, 45, 877-884, 1999.

Dupont, E., C. Cox, S. Shivers, C. Salud, K. Nguyen, A. Cantor, and D. Reintgen, Learning curves and breast cancer lymphatic mapping: institutional volume index, *J Surg Res*, 97, 92-96, 2001.

Early Breast Cancer Trialists' Collaborative Group, Effects of radiotherapy and surgery in early breast cancer: an overview of the randomized trials., *N Engl J Med*, 333, 1444-1455. [Erratum, *N Engl J Med* 1996;1334:1003.], 1995.

Early Breast Cancer Trialists' Collaborative Group, Polychemotherapy for early breast cancer: an overview of the randomised trials, *Lancet*, 352, 930-942, 1998a.

Early Breast Cancer Trialists' Collaborative Group, Tamoxifen for early breast cancer: an overview of the randomised trials, *Lancet*, 351, 1451-1467, 1998b.

Eppenberger-Castori, S., W. Kueng, C. Benz, R. Caduff, Z. Varga, F. Bannwart, D. Fink, H. Dieterich, M. Hohl, H. Muller, K. Paris, F. Schoumacher, and U. Eppenberger, Prognostic and predictive significance of ErbB-2 breast tumor levels measured by enzyme immunoassay, *J Clin Oncol*, 19, 645-656, 2001.

Favret, A. M., R. W. Carlson, D. R. Goffinet, S. S. Jeffrey, F. M. Dirbas, and F. E. Stockdale, Locally advanced breast cancer: is surgery necessary?, *Breast J*, 7, 131-137, 2001.

Field, A. S., N. L. Chamberlain, D. Tran, and A. L. Morey, Suggestions for HER-2/neu testing in breast carcinoma, based on a comparison of immunohistochemistry and fluorescence in situ hybridisation, *Pathology*, 33, 278-282, 2001.

Fisher, B., S. Anderson, C. K. Redmond, N. Wolmark, D. L. Wickerham, and W. M. Cronin, Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer, *N Engl J Med*, 333, 1456-1461, 1995.

Fisher, B., S. Anderson, E. Tan-Chiu, N. Wolmark, D. L. Wickerham, E. R. Fisher, N. V. Dimitrov, J. N. Atkins, N. Abramson, S. Merajver, E. H. Romond, C. G. Kardinal, H. R. Shibata, R. G. Margolese, and W. B. Farrar, 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*, 19, 931-942, 2001.

Fisher, B., S. Anderson, D. L. Wickerham, A. DeCillis, N. Dimitrov, E. Mamounas, N. Wolmark, R. Pugh, J. N. Atkins, F. J. Meyers, N. Abramson, J. Wolter, R. S. Bornstein, L. Levy, E. H. Romond, V. Caggiano, M. Grimaldi, P. Jochimsen, and P. Deckers, 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*, 15, 1858-1869, 1997.

Fisher, B., A. M. Brown, N. V. Dimitrov, and e. 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, *Journal of Clinical Oncology*, 8, 1483-1496, 1990.

Fisher, B., J. Bryant, N. Wolmark, E. Mamounas, A. Brown, E. R. Fisher, D. L. Wickerham, M. Begovic, A. DeCillis, A. Robidoux, R. G. Margolese, A. B. Cruz, Jr., J. L. Hoehn, A. W. Lees, N. V. Dimitrov, and H. D. Bear, Effect of preoperative chemotherapy on the outcome of women with operable breast cancer, *J Clin Oncol*, 16, 2672-2685, 1998a.

Fisher, B., J. P. Costantino, D. L. Wickerham, C. K. Redmond, M. Kavanah, W. M. Cronin, and e. al, Tamoxifen for the prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study, *Journal of the National Cancer Institute*, 90, 1371-1388, 1998b.

Fisher, B., J. Dignam, N. Wolmark, E. Mamounas, J. Costantino, W. Poller, E. R. Fisher, D. L. Wickerham, M. Deutsch, R. Margolese, N. Dimitrov, and M. Kavanah, Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17, *J Clin Oncol*, 16, 441-452, 1998c.

Fisher, B., J. Dignam, N. Wolmark, D. L. Wickerham, E. R. Fisher, E. Mamounas, R. Smith, M. Begovic, N. V. Dimitrov, R. G. Margolese, C. G. Kardinal, M. T. Kavanah, L. Fehrenbacher, and R. H. Oishi,

Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial, *Lancet*, 353, 1993-2000, 1999.

Fleming, J. D., J. S. Cooper, D. E. Henson, and e. et al, *AJCC Cancer Staging Manual, 5th Ed.*, Lippincott-Raven, Philadelphia, 1997.

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*, 19, 602-611, 2001.

Greenlee, R. T., M. B. Hill-Harmon, T. Murray, and M. Thun, Cancer statistics, 2001, *CA Cancer J Clin*, 51, 15-36, 2001.

Group, E. B. C. T. C., Ovarian ablation in early breast cancer: overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group, *Lancet*, 348, 1189-1196, 1996.

Haagensen, C. D., C. Bodian, and D. E. Haagensen, *Breast carcinoma: risk and detection*, 542 pp., WB Saunders, Philadelphia, 1981.

Hellman, S., Stopping metastases at their source, *N Engl J Med*, 337, 996-997, 1997.

Henderson, I. C., D. Berry, G. Demetri, C. Cirincione, L. Goldstein, S. Martion, and et al, Improved disease-free (DFS) and overall survival (OS) from the addition of sequential paclitaxel (T) but not from the escalation of doxorubicin (A) dose level in the adjuvant chemotherapy of patients (pts) with node-positive primary breast cancer (BC). *Proceedings of ASCO*, 17, 101a, 1998.

Hortobagyi, G. N., S. E. Singletary, and E. A. Strom, Treatment of locally advanced and inflammatory breast cancer. in *Diseases of the Breas*, edited by Harris JR, e. a., Lippincott, Williams & Wilkins, Philadelphia, 2000.

Hortobagyi, G. N., R. L. Theriault, A. Lipton, L. Porter, D. Blayney, C. Sinoff, H. Wheeler, J. F. Simeone, J. J. Seaman, R. D. Knight, M. Heffernan, K. Mellars, and D. J. Reitsma, Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group, *J Clin Oncol*, 16, 2038-2044, 1998.

Jensen, M. L., H. Kiaer, J. Andersen, V. Jensen, and F. Melsen, Prognostic comparison of three classifications for medullary carcinomas of the breast, *Histopathology*, 30, 523-532, 1997.

Julien, J. P., N. Bijker, I. S. Fentiman, J. L. Peterse, V. Delledonne, P. Rouanet, A. Avril, R. Sylvester, F. Mignolet, H. Bartelink, and J. A. Van Dongen, Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group, *Lancet*, 355, 528-533, 2000.

Klijn, J. G., R. W. Blamey, F. Boccardo, T. Tominaga, L. Duchateau, and R. Sylvester, 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*, 19, 343-353, 2001.

Knoop, A. S., S. M. Bentzen, M. M. Nielsen, B. B. Rasmussen, and C. Rose, 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*, 19, 3376-3384, 2001.

Krag, D., D. Weaver, T. Ashikaga, F. Moffat, V. S. Klimberg, C. Shriver, S. Feldman, R. Kusminsky, M. Gadd, J. Kuhn, S. Harlow, and P. Beitsch, The sentinel node in breast cancer--a multicenter validation study, *N Engl J Med*, 339, 941-946, 1998.

Lebeau, A., D. Deimling, C. Kaltz, A. Sendelhofert, A. Iff, B. Luthardt, M. Untch, and U. Lohrs, HER-2/neu Analysis in Archival Tissue Samples of Human Breast Cancer: Comparison of Immunohistochemistry and Fluorescence In Situ Hybridization, *J Clin Oncol*, 19, 354-363, 2001.

Levine, M. N., V. H. Bramwell, K. I. Pritchard, B. D. Norris, L. E. Shepherd, H. Abu-Zahra, B. Findlay, D. Warr, D. Bowman, J. Myles, A. Arnold, T. Vandenberg, R. MacKenzie, J. Robert, J. Ottaway, M. Burnell, C. K. Williams, and D. Tu, 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*, 16, 2651-2658, 1998.

Loprinzi, C. L., and S. D. Thome, Understanding the Utility of Adjuvant Systemic Therapy for Primary Breast Cancer, *J Clin Oncol*, 19, 972-979, 2001.

Markiewicz, D. A., D. J. Schultz, J. A. Haas, E. E. Harris, K. R. Fox, J. H. Glick, and L. J. Solin, 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*, 35, 661-668, 1996.

Mass, R., The role of HER-2 expression in predicting response to therapy in breast cancer, *Semin Oncol*, 27, 46-52; discussion 92-100, 2000.

McMasters, K. M., A. E. Giuliano, M. I. Ross, D. S. Reintgen, K. K. Hunt, D. R. Byrd, V. S. Klimberg, P. W. Whitworth, L. C. Tafra, and M. J. Edwards, Sentinel-lymph-node biopsy for breast cancer--not yet the standard of care, *N Engl J Med*, 339, 990-995, 1998.

Menard, S., P. Valagussa, S. Pilotti, L. Gianni, E. Biganzoli, P. Boracchi, G. Tomasic, P. Casalini, E. Marubini, M. I. Colnaghi, N. Cascinelli, and G. Bonadonna, Response to cyclophosphamide, methotrexate, and fluorouracil in lymph node-positive breast cancer according to HER2 overexpression and other tumor biologic variables, *J Clin Oncol*, 19, 329-335, 2001.

Mouridsen, H., M. Gershanovich, Y. Sun, R. Perez-Carrion, C. Boni, A. Monnier, J. Apffelstaedt, R. Smith, H. P. Sleeboom, F. Janicke, A. Pluzanska, M. Dank, D. Becquart, P. P. Bapsy, E. Salminen, R. Snyder, M. Lassus, J. A. Verbeek, B. Staffler, H. A. Chaudri-Ross, and M. Dugan, Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group, *J Clin Oncol*, 19, 2596-2606, 2001.

Muss, H. B., A. D. Thor, D. A. Berry, T. Kute, E. T. Liu, F. Koerner, C. T. Cirrincione, D. R. Budman, W. C. Wood, M. Barcos, and et al., c-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer, *N Engl J Med*, 330, 1260-1266, 1994.

Nabholtz, J. M., A. Buzdar, M. Pollak, W. Harwin, G. Burton, A. Mangalik, M. Steinberg, A. Webster, and M. von Euler, 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*, 18, 3758-3767, 2000.

O'Hea, B. J., A. D. Hill, A. M. El-Shirbiny, S. D. Yeh, P. P. Rosen, D. G. Coit, P. I. Borgen, and H. S. Cody, 3rd, Sentinel lymph node biopsy in breast cancer: initial experience at Memorial Sloan-Kettering Cancer Center, *J Am Coll Surg*, 186, 423-427, 1998.

Overgaard, M., P. S. Hansen, J. Overgaard, C. Rose, M. Andersson, F. Bach, M. Kjaer, C. C. Gadeberg, H. T. Mouridsen, M. B. Jensen, and K. Zedeler, 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*, 337, 949-955, 1997.

Overgaard, M., M. B. Jensen, J. Overgaard, P. S. Hansen, C. Rose, M. Andersson, C. Kamby, M. Kjaer, C. C. Gadeberg, B. B. Rasmussen, M. Blichert-Toft, and H. T. Mouridsen, Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial, *Lancet*, 353, 1641-1648, 1999.

Paik, S., J. Bryant, C. Park, and et al, ErbB-2 and response to doxorubicin in patients with axillary lymph node-positive hormone receptor-negative breast cancer, *J Natl Cancer Inst*, 90, 1361-1370, 1998.

Paik, S., J. Bryant, E. Tan-Chiu, G. Yothers, C. Park, D. L. Wickerham, and N. Wolmark, HER2 and choice of adjuvant chemotherapy for invasive breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-15, *J Natl Cancer Inst*, 92, 1991-1998, 2000.

Pedersen, L., K. Zedeler, S. Holck, T. Schiodt, and H. T. Mouridsen, Medullary carcinoma of the breast, proposal for a new simplified histopathological definition. Based on prognostic observations and

observations on inter- and intraobserver variability of 11 histopathological characteristics in 131 breast carcinomas with medullary features, *Br J Cancer*, 63, 591-595, 1991.

Pegram, M. D., G. Pauletti, and D. J. Slamon, HER-2/neu as a predictive marker of response to breast cancer therapy, *Breast Cancer Res Treat*, 52, 65-77, 1998.

Piccart, M. J., A. Di Leo, M. Beauduin, A. Vindevoghel, J. Michel, C. Focan, A. Tagnon, F. Ries, P. Gobert, C. Finet, M. T. Closon-Dejardin, J. P. Dufrane, J. Kerger, F. Liebens, S. Beauvois, S. Bartholomeus, S. Dolci, J. P. Lobelle, M. Paesmans, and J. M. Nogaret, 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*, 19, 3103-3110, 2001.

Piccart, M. J., A. Di Leo, and A. Hamilton, HER2. a 'predictive factor' ready to use in the daily management of breast cancer patients?, *Eur J Cancer*, 36, 1755-1761, 2000.

Ragaz, J., S. M. Jackson, N. Le, I. H. Plenderleith, and et al, Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer., *N Engl J Med*, 337, 956-962, 1997.

Recht, A., S. B. Edge, L. J. Solin, D. S. Robinson, A. Estabrook, R. E. Fine, G. F. Fleming, S. Formenti, C. Hudis, J. J. Kirshner, D. A. Krause, R. R. Kuske, A. S. Langer, G. W. Sledge, Jr., T. J. Whelan, and D. G. Pfister, Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology, *J Clin Oncol*, 19, 1539-1569, 2001.

Ridolfi, R. L., P. P. Rosen, A. Port, D. Kinne, and V. Mike, Medullary carcinoma of the breast: a clinicopathologic study with 10 year follow-up, *Cancer*, 40, 1365-1385, 1977.

Rosai, J., Borderline epithelial lesions of the breast, *Am J Surg Pathol*, 15, 209-221, 1991.

Rosselli Del Turco, M., D. Palli, A. Cariddi, S. Ciatto, P. Pacini, and V. Distanto, Intensive Diagnostic Follow-up After Treatment of Primary Breast Cancer, *JAMA*, 271, 1593-1597, 1994.

Schnitt, S. J., J. L. Connolly, F. A. Tavassoli, R. E. Fechner, R. L. Kempson, R. Gelman, and D. L. Page, Interobserver reproducibility in the diagnosis of ductal proliferative breast lesions using standardized criteria, *Am J Surg Pathol*, 16, 1133-1143, 1992.

Silverstein, M. J., M. D. Lagios, P. H. Craig, J. R. Waisman, B. S. Lewinsky, W. J. Colburn, and e. al., A prognostic index for ductal carcinoma in situ., *Cancer*, 77, 2267-2274, 1996.

Silverstein, M. J., M. D. Lagios, S. Groshen, J. R. Waisman, B. S. Lewinsky, S. Martino, P. Gamagami, and W. J. Colburn, The influence of margin width on local control of ductal carcinoma in situ of the breast [see comments], *N Engl J Med*, 340, 1455-1461, 1999.

Silvestrini, R., A. Luisi, M. Zambetti, S. Cipriani, P. Valagussa, G. Bonadonna, and M. G. Daidone, Cell proliferation and outcome following doxorubicin plus CMF regimens in node-positive breast cancer, *Int J Cancer*, 87, 405-411, 2000.

Slamon, D. J., B. Leyland-Jones, S. Shak, H. Fuchs, V. Paton, A. Bajamonde, T. Fleming, W. Eiermann, J. Wolter, M. Pegram, J. Baselga, and L. Norton, Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that

overexpresses HER2, *N Engl J Med*, 344, 783-792, 2001.

Smigel, K., Breast cancer death rates decline for white women, *J Natl Cancer Inst*, 87, 173, 1995.

Smith, T. J., N. E. Davidson, D. V. Schapira, E. Grunfeld, H. B. Muss, V. G. Vogel, III, and M. R. Somerfield, American Society of Clinical Oncology 1998 Update of Recommended Breast Cancer Surveillance Guidelines, *J Clin Oncol*, 17, 1080-1082, 1999.

The GIVIO Investigators, Impact of Follow-up Testing on Survival and Health-Related Quality of Life in Breast Cancer, *JAMA*, 271, 1587-1592, 1994.

Theriault, R., A. U. Buzdar, G. N. Hortobagyi, and et al, Irradiation (XRT) following mastectomy in patients treated with FAC adjuvant therapy - M.D. Anderson experience (abstract). *Proc Am Soc Clin Oncol*, 17, 99a, 1998.

Theriault, R. L., A. Lipton, G. N. Hortobagyi, R. Leff, S. Gluck, J. F. Stewart, S. Costello, I. Kennedy, J. Simeone, J. J. Seaman, R. D. Knight, K. Mellars, M. Heffernan, and D. J. Reitsma, 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*, 17, 846-854, 1999.

Thor, A. D., D. A. Berry, and D. R. Budman, ErbB-2, p53, and efficacy of adjuvant therapy in lymph node-positive breast cancer, *J Natl Cancer Inst*, 90, 1346-1360, 1998.

Tubbs, R. R., J. D. Pettay, P. C. Roche, M. H. Stoler, R. B. Jenkins, and T. M. Grogan, Discrepancies in clinical laboratory testing of eligibility for trastuzumab therapy: apparent immunohistochemical

false-positives do not get the message, *J Clin Oncol*, 19, 2714-2721, 2001.

Vergote, I., J. Bonnetterre, B. Thurlimann, J. Robertson, M. Krzakowski, L. Mauriac, L. Koralewski, A. Webster, M. Steinberg, and M. von Euler, Randomised study of anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women, *Eur J Cancer*, 36 Suppl 4, S84-85, 2000.

Veronesi, U., G. Paganelli, V. Galimberti, G. Viale, S. Zurrada, M. Bedoni, A. Costa, C. de Cicco, J. G. Geraghty, A. Luini, V. Sacchini, and P. Veronesi, Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes, *Lancet*, 349, 1864-1867, 1997.

Veronesi, U., B. Salvadori, A. Luini, M. Greco, R. Saccozzi, M. del Vecchio, L. Mariani, S. Zurrada, and F. Rilke, Breast conservation is a safe method in patients with small cancer of the breast. Long-term results of three randomised trials on 1,973 patients, *Eur J Cancer*, 31A, 1574-1579, 1995.

Vogel, C., M. A. Cobleigh, D. Tripathy, J. C. Gutheil, L. N. Harris, L. Fehrenbacher, D. J. Slamon, M. Murphy, W. F. Novotny, M. Burchmore, S. Shak, and S. J. Stewart, First-line, single-agent Herceptin(R) (trastuzumab) in metastatic breast cancer. a preliminary report, *Eur J Cancer*, 37 Suppl 1, 25-29, 2001.

Wang, S., M. H. Saboorian, E. Frenkel, L. Hynan, S. T. Gokaslan, and R. Ashfaq, 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*, 53, 374-381, 2000.

Wood, W. C., D. R. Budman, A. H. Korzun, M. R. Cooper, J. Younger, R. D. Hart, A. Moore, J. A. Ellerton, L. Norton, C. R. Ferree, and et al., Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma, *N Engl J Med*, 330, 1253-1259, 1994.