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Continue
Breast Cancer

Table of Contents

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Noninvasive Breast Cancer
• Lobular Carcinoma In Situ (LCIS-1)
• Ductal Carcinoma In Situ (DCIS-1)

Invasive Breast Cancer
• Clinical Stage, Workup (BINV-1)
• Locoregional Treatment of Clinical Stage I, IIA, or IIB Disease or T3,N1,M0 (BINV-2)
• Systemic Adjuvant Treatment (BINV-4)
• Preoperative Chemotherapy Guideline
  › Clinical Stage IIA, IIB, Workup (BINV-10)
  › Primary Treatment, Adjuvant Treatment (BINV-11)
  › Clinical Stage IIIA, IIB, IIIC, and Stage IV, Workup (BINV-13)
  › Preoperative Chemotherapy, Locoregional Treatment, Adjuvant Treatment (BINV-14)
• Surveillance/Follow-Up, Recurrence Workup or Initial Workup for Stage IV Disease (BINV-15)
• Treatment of Recurrence/Stage IV Disease (BINV-16)
• Follow-up Therapy for Hormone Treatment of Recurrence/Stage IV (BINV-17)

Invasive Breast Cancer (continued)
• Principles of HER2 Testing (BINV-A)
• Principles of Dedicated Breast MRI Testing (BINV-B)
• Surgical Axillary Staging - Stage I, IIA, and IIB (BINV-C)
• Axillary Lymph Node Staging (BINV-D)
• Margin Status in Infiltrating Carcinoma (BINV-E)
• Special Considerations to Breast-Conserving Therapy Requiring Radiation Therapy (BINV-F)
• Adjuvant Hormonal Therapy (BINV-G)
• Adjuvant Chemotherapy (BINV-H)
• Definition of Menopause (BINV-I)
• Subsequent Hormonal Therapy (BINV-J)
• Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-K)

Special Considerations
• Phyllodes Tumor (PHYLL-1)
• Paget’s Disease (PAGET-1)
• Breast Cancer During Pregnancy (PREG-1)

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Summary of the Guidelines Updates

Summary of changes in the 2.2007 version of the Breast Guidelines from the 1.2007 version include:

- Based on FDA approval and data from a recent Phase III study of lapatinib plus capecitabine for HER2 positive advanced breast cancer, the Panel added the following footnote for patients with HER2-positive breast cancer that is hormone receptor-negative, symptomatic visceral disease, or hormone refractory (See BINV-16):
  "Lapatinib plus capecitabine is an option in patients previously treated with an anthracycline, taxane, and trastuzumab."

Summary changes in the 1.2007 version of the Breast Guidelines from the 2.2006 version include:

- Based on results from the NSABP Study of Tamoxifen and Raloxifene (STAR) trial, the Panel added raloxifene as an option for reducing the risk of invasive breast cancer in postmenopausal women with lobular carcinoma in situ (See LCIS-1).
- Footnotes c and d are new to page LCIS-1.
- Margin status in DCIS (See DCIS-A). With respect to pathologic margins between 1-10 mm, wider margins are generally associated with lower local recurrence rates. However, close surgical margins (<1mm) at the fibroglandular boundary of the breast (chest wall or skin) do not mandate surgical re-excision but can be an indication for higher boost dose radiation to the involved lumpectomy site. (category 2B)
- The accuracy of HER2 assays used in clinical practice is a major concern, and results from several studies have shown that false-positive and false-negative HER2 test results are common. An NCCN Task Force reviewed this topic and issued recommendations which are summarized in the Principles of HER2 Testing (See BINV-A).
- When breast MRI is indicated, it should be performed and interpreted by a expert breast imaging team working in concert with the multidisciplinary treatment team. The Panel recommendations for breast MRI testing are listed on page BINV-B.
- Sentinel node mapping and excision is now listed as preferred over axillary dissection level I/II (See BINV-C).
- Footnote 5 is new to page BINV-C.
- Sentinel lymph node biopsy is the preferred method of axillary lymph node staging (See BINV-D).
- Special considerations to breast-conserving therapy requiring radiation therapy (See BINV-F) has been updated to include the following relative contraindication: Women ≤ 35 y or premenopausal women with a known BRCA 1/2 mutation:
  ▶ Have an increased risk of ipsilateral breast recurrence or contralateral breast cancer with breast conserving therapy
  ▶ Prophylactic bilateral mastectomy for risk reduction may be considered.
- Recent studies document the substantial improvement in outcome with the incorporation of trastuzumab in adjuvant treatment of HER2 positive breast cancer The guideline includes specific representative doses and schedules for the recommended adjuvant chemotherapy regimens (See BINV-H). A number of chemotherapy regimens have been studied as preoperative chemotherapy. The Panel believes that the regimens listed in the adjuvant setting are also appropriate to consider in the neoadjuvant setting.
- Treatment of recurrence (See BINV-I) ± hyperthermia was added as a category 3 recommendation.
- Aromatase inhibitors are not active in the treatment of women with functioning ovaries and should not be used in women with intact ovarian function. The assessment of ovarian function in women experiencing treatment-induced amenorrhea is difficult and requires re-evaluation over time. This has been elaborated in the Definition of Menopause (See BINV-I).

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

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Lobular Carcinoma in Situ

**DIAGNOSIS**

- Lobular carcinoma in situ (LCIS)
- Stage 0
  - Tis, N0, M0

**WORKUP**

- H&P
- Diagnostic bilateral mammogram
- Pathology review

**PRIMARY TREATMENT**

- Observation

**RISK REDUCTION**

- Counseling regarding risk reduction with tamoxifen for premenopausal women, or with tamoxifen or raloxifene for postmenopausal women (category 1), see the NCCN Breast Cancer Risk Reduction Guidelines.
- In special circumstances, bilateral mastectomy ± reconstruction may be considered for risk reduction

**SURVEILLANCE/FOLLOW-UP**

- 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

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---

*a* See NCCN Breast Cancer Screening and Diagnosis Guidelines.

*b* The panel endorses the College of American Pathology Protocol for pathology reporting for all invasive and non-invasive carcinomas of the breast.


*c* Histologically aggressive variants of LCIS (pleomorphic LCIS) may have a similar biological behavior to that of DCIS, but outcome data regarding the efficacy of surgical excision to negative margins and/or radiotherapy are lacking.

*d* Some serotonin reuptake inhibitors decrease the formation of endoxifen, an active metabolite of tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. The clinical impact of these observations is not known.
Ductal Carcinoma in Situ

**DIAGNOSIS**

- Ductal carcinoma in situ (DCIS) Stage 0
  - Tis, N0, M0

**WORKUP**

- H&P
- Diagnostic bilateral mammogram
- Pathology review
- Determination of tumor estrogen receptor (ER) status

**PRIMARY TREATMENT**

- Lumpectomy without lymph node dissection + RT or Total mastectomy without lymph node dissection ± reconstruction

- Lumpectomy + RT or Total mastectomy without lymph node dissection ± reconstruction or Lumpectomy alone (category 2B)

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**Notes:**

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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.

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**See NCCN Breast Cancer Screening and Diagnosis Guidelines.**

**See Margin Status in DCIS (DCIS-A).**

**See Special Considerations Breast-Conserving Therapy (BINV-F).**

**See Postsurgical Treatment (DCIS-2).**

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**See Margin Status in DCIS (DCIS-A).**

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**See Margin Status in DCIS (DCIS-A).**
DCIS POSTSURGICAL TREATMENT

Adjuvant treatment:
Consider tamoxifen\(^1\) for 5 years for:
- Patients treated with breast-conserving therapy (lumpectomy) and RT (category 1)\(^m\), especially for those with ER-positive DCIS. The benefit of tamoxifen for ER-negative DCIS is uncertain
- Patients treated with excision alone \(^m\)

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

SURVEILLANCE/FOLLOW-UP

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

\(^1\)Some serotonin reuptake inhibitors decrease the formation of endoxifen, an active metabolite of tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. The clinical impact of these observations is not known.

\(^m\)Available data suggest tamoxifen provides risk reduction in the ipsilateral breast treated with breast conservation and in the contralateral breast in patients with mastectomy or breast conservation with ER-positive primary tumors. 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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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. With pathologic margins between 1-10 mm, wider margins are generally associated with lower local recurrence rates. However, close surgical margins (<1mm) at the fibroglandular boundary of the breast (chest wall or skin) do not mandate surgical re-excision but can be an indication for higher boost dose radiation to the involved lumpectomy site. (category 2B)
### Clinical Stage

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1, N0, M0</td>
<td>• H&amp;P</td>
</tr>
<tr>
<td>or</td>
<td>• CBC, platelets</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>• Liver function tests</td>
</tr>
<tr>
<td>T0, N1, M0</td>
<td>• Chest imaging</td>
</tr>
<tr>
<td>T1, N1, M0</td>
<td>• Diagnostic bilateral mammogram, ultrasound as necessary</td>
</tr>
<tr>
<td>T2, N0, M0</td>
<td>• Pathology review&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>or</td>
<td>• Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER2 status&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>• Breast MRI (optional)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>T2, N1, M0</td>
<td>• Bone scan (optional) (Indicated if localized symptoms or elevated alkaline phosphatase or if T3, N1, M0) (category 2B)</td>
</tr>
<tr>
<td>T3, N0, M0</td>
<td>• Abdominal CT or US or MRI (optional for stage IIA or IIB, indicated if elevated alkaline phosphatase, abnormal LFTs, abdominal symptoms, abnormal physical examination of the abdomen, or if T3, N1, M0) (category 2B)</td>
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<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>T3, N1, M0</td>
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</table>

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<sup>a</sup> The panel endorses the College of American Pathology Protocol for pathology reporting for all invasive and non-invasive carcinomas of the breast. [http://www.cap.org/apps/docs/cancer_protocols/protocols_index.html](http://www.cap.org/apps/docs/cancer_protocols/protocols_index.html)

<sup>b</sup> See Principles of HER2 Testing (BINV-A).  

<sup>c</sup> See Principles of Dedicated Breast MRI Testing (BINV-B).  

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**BINV-1**
LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3, N1, M0

- RT to whole breast with boost\(^h\) (by photons, brachytherapy, or electron beam) to tumor bed and supraclavicular area (category 1). Consider RT to internal mammary nodes\(^i\) (category 3). RT may be given concurrent with CMF (category 2B) or follow chemotherapy when chemotherapy indicated.

- RT to whole breast with boost\(^h\) (by photons, brachytherapy, or electron beam) to tumor bed (category 1). Consider RT to supraclavicular area (category 2B). Consider RT to internal mammary nodes\(^i\) (category 3). RT may be given concurrent with CMF (category 2B) or follow chemotherapy when chemotherapy indicated.

- RT to whole breast with boost\(^h\) (by photons, brachytherapy, or electron beam) to tumor bed. RT may be given concurrent with CMF (category 2B) or follow chemotherapy when chemotherapy indicated.

Lumpectomy with surgical axillary staging (category 1)\(^d,e,f\)

- 1-3 positive axillary nodes

- Negative axillary nodes

Total mastectomy with surgical axillary staging\(^d,e\) (category 1) ± reconstruction

If T2 or T3 and fulfills criteria for breast conserving therapy except for size\(^f\)

- Consider Preoperative Chemotherapy Guideline (BINV-10)

\(^d\) See Surgical Axillary Staging (BINV-C).
\(^e\) See Axillary Lymph Node Staging (BINV-D) and Margin Status in Infiltrating Carcinoma (BINV-E).
\(^f\) See Special Considerations to Breast-Conserving Therapy (BINV-F).
\(^g\) Consideration may be given to additional staging including bone scan and abdominal CT/US/MRI; chest CT (category 2B).
\(^h\) Whole breast irradiation with boost (by photons, brachytherapy or electron beam) to tumor bed. Boost to tumor bed is especially encouraged in those 50 y of age or younger. Partial breast irradiation should be performed only as part of a high quality prospective clinical trial.
\(^i\) RT should be given to the internal mammary lymph nodes if they are clinically or pathologically positive, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be utilized in all cases where RT is delivered to the internal mammary lymph nodes.

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

- **Total mastectomy with surgical axillary staging**
  - ≥ 4 positive axillary nodes
    - Postchemotherapy RT to chest wall + supraclavicular area (category 1). Consider RT to internal mammary nodes (category 3)
  - 1-3 positive axillary nodes
    - Consider postchemotherapy RT to chest wall + supraclavicular area (category 1); if RT is given, consider internal mammary RT (category 3). 
  - Negative axillary nodes and tumor > 5 cm or margins positive
    - Postchemotherapy RT to chest wall. Consider RT to supraclavicular area (category 2B) Consider RT to internal mammary nodes (category 3).
  - Negative axillary nodes and tumor ≤ 5 cm and margins close (< 1mm)
    - Consider RT to chest wall
  - Negative axillary nodes and tumor ≤ 5 cm and margins ≥ 1mm
    - No RT

- **RT** should be given to the internal mammary lymph nodes that are clinically or pathologically positive, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be utilized in all cases where RT is delivered to the internal mammary lymph nodes.

- There is inconsistent high-level evidence of survival benefit in this subset.

- **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.

---

See Surgical Axillary Staging (BINV-C).
See Axillary Lymph Node Staging (BINV-D) and Margin Status in Infiltrating Carcinoma (BINV-E).
Consideration may be given to additional staging including bone scan; abdominal CT/US/MRI; chest CT (category 2B).
RT should be given to the internal mammary lymph nodes that are clinically or pathologically positive, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be utilized in all cases where RT is delivered to the internal mammary lymph nodes.
There is inconsistent high-level evidence of survival benefit in this subset.
Invasive Breast Cancer

<table>
<thead>
<tr>
<th>HISTOLOGY</th>
<th>HORMONE RECEPTOR STATUS</th>
<th>HER2 STATUS</th>
<th>SYSTEMIC ADJUVANT TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal, NOS</td>
<td>ER-positive and/or PR positive</td>
<td>HER2 positive b</td>
<td>See Systemic Adjuvant Treatment - Hormone Receptor Positive - HER2 Positive Disease (BINV-5)</td>
</tr>
<tr>
<td>Lobular</td>
<td></td>
<td>HER2 negative b</td>
<td>See Systemic Adjuvant Treatment - Hormone Receptor Positive - HER2 Negative Disease (BINV-6)</td>
</tr>
<tr>
<td>Mixed</td>
<td></td>
<td></td>
<td>See Systemic Adjuvant Treatment - Hormone Receptor Negative - HER2 Positive Disease (BINV-7)</td>
</tr>
<tr>
<td>Metaplastic</td>
<td></td>
<td></td>
<td>See Systemic Adjuvant Treatment - Hormone Receptor Negative - HER2 Negative Disease (BINV-8)</td>
</tr>
<tr>
<td>Tubular</td>
<td>ER-positive and/or PR positive</td>
<td>HER2 positive b</td>
<td>See Systemic Adjuvant Treatment - Favorable Histologies (BINV-9)</td>
</tr>
<tr>
<td>Colloid</td>
<td></td>
<td>HER2 negative b</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ER-negative and PR-negative</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

See Principles of HER2 Testing (BINV-A).

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.
**SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR POSITIVE - HER2 POSITIVE DISEASE**

- **ER-positive and/or PR-positive and HER2 positive**
  - **Histology:**
    - Ductal, NOS
    - Lobular
    - Mixed
    - Metaplastic

- **Node positive (one or more metastases > 2 mm to one or more ipsilateral axillary lymph nodes)**

- **Tumor ≤ 0.5 cm or**
  - Microinvasive or
  - Tumor 0.6-1.0 cm, well differentiated

- **Tumor 0.6-1.0 cm, moderate/poorly differentiated or unfavorable features**

- **Tumor > 1 cm**

- **pN0** → **No adjuvant therapy**
- **pN1mi** → **Consider adjuvant hormonal therapy**
- **Adjuvant hormonal therapy**
  - ± adjuvant chemotherapy (category 1)
- **Adjuvant hormonal therapy**
  - + adjuvant chemotherapy + trastuzumab (category 1)

---

See [Adjuvant Hormonal Therapy (BINV-G)] and [Adjuvant Chemotherapy (BINV-H)]

---

**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.
SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR POSITIVE - HER2 NEGATIVE DISEASE

**ER-positive and/or PR-positive and HER2 negative**

**Histology:**
- Ductal, NOS
- Lobular
- Mixed
- Metaplastic

**Tumor >1 cm**

**pT1, pT2, or pT3; and pN0 or pN1mi (≤ 2 mm axillary node metastasis)**

**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.
SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR NEGATIVE - HER2 POSITIVE DISEASE

ER-negative and PR-negative and HER2 positive

Histology:
- Ductal, NOS
- Lobular
- Mixed
- Metaplastic

Node positive (one or more metastases > 2 mm to one or more ipsilateral axillary lymph nodes)

See Principles of HER2 Testing (BINV-A).

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

There are insufficient data to make chemotherapy recommendations for those over 70 y old. Treatment should be individualized with consideration of comorbid conditions.

See Adjuvant Hormonal Therapy (BINV-G) and Adjuvant Chemotherapy (BINV-H)

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.
SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR NEGATIVE - HER2 NEGATIVE DISEASE

- ER-negative and PR-negative and HER2 negative
  - Histology:
    - Ductal, NOS
    - Lobular
    - Mixed
    - Metaplastic
  - Node positive (one or more metastases > 2 mm to one or more ipsilateral axillary lymph nodes)

See Adjuvant Hormonal Therapy (BINV-G) and Adjuvant Chemotherapy (BINV-H)

**See Principles of HER2 Testing (BINV-A).**

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

There are insufficient data to make chemotherapy recommendations for those over 70 y old. Treatment should be individualized with consideration of comorbid conditions.

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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.
Invasive Breast Cancer

SYSTEMIC ADJUVANT TREATMENT - FAVORABLE HISTOLOGIES

<table>
<thead>
<tr>
<th>Histology</th>
<th>Node positive (one or more metastasis &gt; 2 mm to one or more ipsilateral axillary lymph nodes)</th>
<th>Node positive (one or more metastasis &gt; 2 mm to one or more ipsilateral axillary lymph nodes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER-positive and/or PR-positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubular</td>
<td>Consider adjuvant hormonal therapy</td>
<td></td>
</tr>
<tr>
<td>Colloid</td>
<td>Consider adjuvant chemotherapy</td>
<td></td>
</tr>
<tr>
<td>ER-negative and PR-negative</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

See Adjuvant Hormonal Therapy (BINV-G) and Adjuvant Chemotherapy (BINV-H)

If ER-positive consider hormonal therapy for risk reduction and to diminish the small risk of disease recurrence.

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

See Adjuvant Hormonal Therapy (BINV-G).

Chemotherapy and hormonal therapy used as adjuvant therapy should be given sequentially with hormonal therapy following chemotherapy. The benefits of chemotherapy and of hormonal therapy are additive. However, the absolute benefit from chemotherapy may be small. The decision to add chemotherapy to hormonal therapy should be individualized, especially in those with a favorable prognosis and in women age ≥ 60 y where the incremental benefit of chemotherapy may be smaller. Available data suggest sequential or concurrent hormonal therapy with RT is acceptable.

There are insufficient data to make chemotherapy recommendations for those over 70 y old. Treatment should be individualized with consideration of comorbid conditions.

See text paragraph for medullary carcinoma (MS-21).
Preoperative Chemotherapy Guideline

CLINICAL STAGE

Stage IIA
T2, N0, M0

Stage IIB
T2, N1, M0
T3, N0, M0

Stage IIIA
T3, N1, M0

and

Fulfills criteria for breast conserving surgery except for tumor size

WORKUP

- H&P
- CBC, platelets
- Liver function tests
- Chest imaging
- Diagnostic bilateral mammogram, ultrasound as necessary
- Pathology review
- Determination of tumor ER/PR status and HER2 status\(^b\)
- Breast MRI (optional)\(^c\)
- Bone scan (optional) (indicated if localized symptoms or elevated alkaline phosphatase or if T3, N1, M0) (category 2B)
- Abdominal CT or US or MRI (optional for stage IIA or IIB, indicated if elevated alkaline phosphatase, abnormal LFTs, abdominal symptoms, abnormal physical examination of the abdomen, or if T3, N1, M0) (category 2B)

\(^b\) See Principles of HER2 Testing (BINV-A).
\(^c\) See Principles of Dedicated Breast MRI Testing (BINV-B).

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.
Preoperative Chemotherapy Guideline

**PRIMARY TREATMENT**

- No response after 3-4 cycles or Progressive disease
  - Consider alternative chemotherapy
  - Partial response, lumpectomy not possible
  - Partial response, lumpectomy possible or Complete response
  - See Lumpectomy Pathway (BINV-12)

- No response after 3-4 cycles or Progressive disease
  - See Mastectomy Pathway (BINV-12)

---

**Desires breast preservation**

- Core biopsy of breast tumor, consider FNA of clinically positive axillary lymph node(s) or sentinel lymph node procedure if clinically negative axillary lymph node(s)
  - Localization of tumor bed for future surgical management
  - Preoperative chemotherapy (Hormonal therapy alone may be considered for receptor positive disease in postmenopausal patients)

- Partial response, lumpectomy possible or Complete response

---

**Does not desire breast preservation**

- See Stage I and II breast cancer (BINV-1 and BINV-2)

---

See Surgical Axillary Staging (BINV-C).

A number of combination and single agent chemotherapy regimens have activity in the preoperative setting. In general, those chemotherapy regimens recommended in the adjuvant setting (See BINV-H) may be considered in the preoperative setting. If treated with hormonal therapy, an aromatase inhibitor is preferred for postmenopausal women.

Patients with HER2 positive tumors should be considered for preoperative chemotherapy incorporating trastuzumab (See BINV-H).

Definition of Menopause (See BINV-I).

---

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.
**Preoperative Chemotherapy Guideline**

**LOCAL TREATMENT**

Mastectomy and surgical axillary staging\(x\) ± reconstruction. If sentinel lymph node biopsy performed prechemotherapy and negative findings, may omit axillary lymph node dissection

Lumpectomy with surgical axillary staging.\(x\)

If sentinel lymph node biopsy performed prechemotherapy and negative findings, may omit axillary lymph node dissection

\[\text{Consider additional chemotherapy}\]

**ADJUVANT TREATMENT**

- Adjuvant RT post-mastectomy is based on prechemotherapy tumor characteristics as per BINV-3\(y\)
- Adjuvant RT post-lumpectomy based on prechemotherapy tumor characteristics as per BINV-2\(y\)
- Hormonal therapy if ER-positive (category 1)\(^p,q\)

**See Adjuvant Hormonal Therapy (BINV-G)**

\(^p\) See Adjuvant Hormonal Therapy (BINV-G).

\(^q\) Chemotherapy and hormonal therapy used as adjuvant therapy should be given sequentially with hormonal therapy following chemotherapy. The benefits of chemotherapy and of hormonal therapy are additive. However, the absolute benefit from chemotherapy may be small. The decision to add chemotherapy to hormonal therapy should be individualized, especially in those with a favorable prognosis and in women age ≥ 60 y where the incremental benefit of chemotherapy may be smaller. Available data suggest sequential or concurrent hormonal therapy with RT is acceptable.

\(^x\) Axillary staging may include sentinel node biopsy (category 3) or level I/II dissection.

\(^y\) Whole breast irradiation with boost (by photons, brachytherapy or electron beam) to tumor bed. Boost to tumor bed is especially encouraged in those 50 y of age or younger. If internal mammary lymph nodes are clinically or pathologically positive, RT should be given to the internal mammary nodes, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be utilized in all cases where RT is delivered to the internal mammary lymph node field.

**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.
# Locally Advanced Invasive Breast Cancer

## Clinical Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Workup</th>
</tr>
</thead>
</table>
| IIIA  | T0, N2, M0  
T1, N2, M0  
T2, N2, M0  
T3, N2, M0  
*(Stage IIIA patients with T3, N1, M0 disease, see BINV-1)* | H&P  
CBC, platelets  
Liver function tests  
Chest imaging  
Pathology review  
Prechemotherapy determination of tumor ER/PR receptor status and HER2 status  
Diagnostic bilateral mammogram, ultrasound as necessary  
Bone scan (category 2B)  
Abdominal CT or US or MRI (category 2B)  
Breast MRI (optional)* |
| IIIB  | T4, N0, M0  
T4, N1, M0  
T4, N2, M0 | |
| IIIC  | Any T, N3, M0 | |
| IV    | Any T, any N, M1 | See Initial Workup for Stage IV Disease (BINV-15) |

*See Principles of Dedicated Breast MRI Testing (BINV-B).*

**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.
**Invasive Breast Cancer**

**PREOPERATIVE CHEMOTHERAPY FOR LOCALLY ADVANCED INVASIVE BREAST CANCER**

- Doxorubicin- or epirubicin-based or paclitaxel- or docetaxel-based preoperative chemotherapy preferred

**_RESPONSE**

- If response → Consider additional systemic chemotherapy and/or preoperative radiation
- If no response → Individualized treatment

**LOCOREGIONAL TREATMENT**

- Total mastectomy + surgical axillary staging + RT to chest wall and supraclavicular nodes (plus internal mammary nodes if involved) ± delayed breast reconstruction

**ADJUVANT TREATMENT**

- Additional chemotherapy + hormonal therapy if estrogen receptor positive

---

**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.

---

**Explanation:**

- A number of combination and single agent chemotherapy regimens have activity in the preoperative setting. In general, those chemotherapy regimens recommended in the adjuvant setting may be considered in the preoperative setting. If treated with hormonal therapy, an aromatase inhibitor is preferred for postmenopausal women.

- Patients with HER2 positive tumors should be considered for preoperative chemotherapy incorporating trastuzumab.

- There are no data regarding breast conserving surgery in the management of inflammatory breast cancer.
SURVEILLANCE/FOLLOW-UP

- Interval history and physical exam every 4-6 mo for 5 y, then every 12 mo
- Mammogram every 12 mo (and 6-12 mo post-RT if breast conserved) (category 2B)
- Women on tamoxifen: annual gynecologic assessment every 12 mo if uterus present
- Women on an aromatase inhibitor or who experience ovarian failure secondary to treatment should have monitoring of bone health
- Assess and encourage adherence to adjuvant hormonal therapy.

RECURRENT WORKUP or INITIAL WORKUP FOR STAGE IV DISEASE

- H&P
- CBC, platelets
- Liver function tests
- Chest imaging
- Bone scan
- X-rays of symptomatic bones and long and weight-bearing bones abnormal on bone scan
- Consider abdominal CT or MRI
- Biopsy documentation of first recurrence, if possible
- Consider determination of tumor ER/PR and HER2 status if unknown, originally negative or not over-expressed\(^b\)
- PET scan (optional)(category 2B)

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.

\(a\) See Principles of HER2 Testing (BINV-A).

\(b\) See NCCN Palliative Care Guidelines.

\(aa\) Pamidronate or zoledronic acid (with calcium citrate 500 mg and vitamin D 400 IU supplement) should be given (category 1) in addition to chemotherapy or hormonal therapy if bone metastasis present, expected survival ≥ 3 months, and creatinine < 3.0 mg/dL.

\(bb\) See Treatment of Recurrence/Stage IV Disease (BINV-16).
Invasive Breast Cancer

TREATMENT OF RECURRENCE/STAGE IV DISEASE

Local recurrence

Initial treatment with mastectomy

Surgical resection (if possible) + RT (if possible)

Consider systemic therapy

Initial treatment with lumpectomy + RT

Mastectomy

Consider systemic therapy

ER/PR positive or bone/soft tissue only or asymptomatic visceral disease

Prior antiestrogen within 1 y

Second-line hormonal therapy

Aromatase inhibitor or Antiestrogen

No prior antiestrogen or > 1 y off antiestrogen

Premenopausal

Ovarian ablation or suppression, plus hormonal therapy as for postmenopausal women or Antiestrogen

HER2\(^b\) positive

Trastuzumab ± chemotherapy

HER2\(^b\) negative

Chemotherapy

No response to 3 sequential regimens or ECOG performance status ≥ 3

Consider no further cytotoxic therapy

ER/PR negative or symptomatic visceral or hormone refractory disease

TREATMENT OF RECURRENCE

Surgery, radiation ± hyperthermia (category 3 for hyperthermia), or regional chemotherapy (e.g., intrathecal methotrexate) indicated for localized clinical scenarios:

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

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See Principles of HER2 Testing (BINV-A).

Definition of Menopause (See BINV-I).

Pamidronate or zoledronic acid (with calcium citrate 500 mg and vitamin D 400 IU supplement) should be given (category 1) in addition to chemotherapy or hormonal therapy if bone metastasis present, expected survival ≥ 3 mo, and creatinine < 3.0 mg/dL.

The value of continued trastuzumab following progression on first line-trastuzumab containing chemotherapy for metastatic breast cancer is unknown. The optimal duration of trastuzumab in patients with long-term control of disease is unknown.

Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity.

Lapatinib plus capecitabine is an option in patients previously treated with an anthracycline, taxane, and trastuzumab.
FOLLOW-UP THERAPY FOR HORMONE TREATMENT OF RECURRENCE/STAGE IV DISEASE

1. Continue hormonal therapy until progression or unacceptable toxicity → Progression → No clinical benefit after 3 consecutive hormonal therapy regimens or Symptomatic visceral disease
   - Yes → Chemotherapy (As in BINV-16)
   - No → Trial of new hormone therapy

2. No response to hormonal therapy → Chemotherapy (As in BINV-16)

---

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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.

---

**See Subsequent Hormonal Therapy (BINV-J).**

**See Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-K).**

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.
**PRINCIPLES OF HER2 TESTING**

1. **Initial testing by IHC**
   - If the laboratory meets quality assurance standards for IHC HER2 testing methodology:
     - **Yes**: IHC testing
       - IHC 0, 1+ → HER2 (-)
       - IHC 2+ → Borderline result
       - IHC 3+ → HER2 (+)
     - **No**: Send sample to reference laboratory
   - **No**: Send sample to reference laboratory

2. **Initial testing by FISH**
   - If the laboratory meets quality assurance standards for FISH HER2 testing methodology:
     - **Yes**: FISH testing
       - FISH (-) → HER2 (-)
       - FISH+ → Borderline result
       - Count additional cells
     - **No**: Send sample to reference laboratory
     - **Borderline result**: FISH retest
     - **Borderline result**: HER2 (+)

---

2. HER2 testing should be done only in laboratories accredited to perform such testing. Ongoing proficiency testing and full reporting of HER2 assay methods and results are required. A laboratory may perform only those tests which have been demonstrated to conform to these quality assurance standards. All other HER2 testing should be sent to a qualified reference laboratory.

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

4. Borderline IHC samples (eg, IHC 2+) are subjected to reflex testing by a validated complementary (eg, FISH) method that has shown at least 95% concordance between IHC 0, 1+ results and FISH non-amplified results, and IHC 3+ results and FISH amplified results for 50-100 samples (where at least half of the cases represent HER2 positive tumors).

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

---

**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.
PRINCIPLES OF DEDICATED BREAST MRI TESTING

Personnel, facility and equipment

• Breast MRI examinations should be performed and interpreted by an expert breast imaging team working in concert with the multidisciplinary treatment team.

• Breast MRI examinations require a dedicated breast coil and breast imaging radiologists familiar with the optimal timing sequences and other technical details for image interpretation. The imaging center should have the ability to perform MRI guided needle sampling and/or wire localization of MRI detected findings.

Clinical indications and applications

• Breast MRI examination is an adjunct to other breast imaging and should not be used in lieu of standard breast imaging with mammography and ultrasound.

• For patients with biopsy proven adenocarcinoma presenting in the axilla, a normal clinical breast exam and negative mammogram (TxN1-3), breast MRI examination is indicated to attempt to identify a primary cancer in the breast.

• Breast MRI may be considered for a patient with biopsy-proven breast cancer, when dense breast tissue precludes assessment for extent of disease.

• Breast MRI may be useful in defining the extent of cancer, the presence of multicentric cancer in women with dense breast tissue on mammography, and extent of disease in women with locally advanced breast cancer. Decision making regarding the extent of breast surgery (e.g. breast conservation therapy vs. mastectomy) should not be made solely on the basis of MRI and may require additional tissue sampling of areas of concern identified by breast MRI.
**SURGICAL AXILLARY STAGING - STAGE I, IIA, AND IIB**

Clinical Stage I/II

- Sentinel lymph node candidate - Meeting ALL of the following criteria:
  - No prior chemotherapy or hormonal therapy
  - Experienced sentinel node team

<table>
<thead>
<tr>
<th>Clinical Stage I/II</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior chemotherapy or hormonal therapy</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Experienced sentinel node team</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Sentinel lymph node candidate**

- Refer to experienced sentinel node team or Axillary dissection level I/II
- Axillary dissection level I/II

**Sentinel node positive at time of diagnosis**

- FNA or core biopsy negative

**Sentinel node negative**

- No further surgery
- Axillary dissection level I/II

**Sentinel node not identified**

- Axillary dissection level I/II

---

1. Sentinel node team must have documented experience with sentinel node biopsy in breast cancer. Team includes surgeon, radiologists, nuclear medicine physician, pathologist, and prior discussion with medical and radiation oncologists on use of sentinel node for treatment decisions.

2. Consider pathologic confirmation of malignancy in clinically positive nodes using ultrasound guided FNA or core biopsy in determining if patient needs axillary lymph node dissection.

3. Axillary sentinel node biopsy in all cases; internal mammary sentinel node biopsy optional if drainage maps to internal mammary nodes (category 3).

4. Sentinel lymph node mapping injections may be peritumoral, subareolar or subdermal. However, only peritumoral injections map to the internal mammary lymph node(s).

5. Results of randomized clinical trials indicate that there is a lower risk of morbidity associated with sentinel node mapping and excision than with level I/II axillary dissection.

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

---

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.
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 II nodes.

Sentinel lymph node biopsy is the preferred method of axillary lymph node staging if there is an experienced sentinel node team and the patient is an appropriate sentinel lymph node biopsy candidate (See BINV-C).
MARGIN STATUS IN INFILTRATING CARCINOMA

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

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

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

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

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

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.
### SPECIAL CONSIDERATIONS TO BREAST-CONSERVING THERAPY REQUIRING RADIATION THERAPY

<table>
<thead>
<tr>
<th>Contraindications for breast-conserving therapy requiring radiation therapy include:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absolute:</strong></td>
</tr>
<tr>
<td>• Prior RT to the breast or chest wall</td>
</tr>
<tr>
<td>• RT during pregnancy</td>
</tr>
<tr>
<td>• Diffuse suspicious or malignant appearing microcalcifications</td>
</tr>
<tr>
<td>• Widespread disease that cannot be incorporated by local excision through a single incision that achieves negative margins with a satisfactory cosmetic result.</td>
</tr>
<tr>
<td>• Positive pathologic margin[^1]</td>
</tr>
<tr>
<td><strong>Relative:</strong></td>
</tr>
<tr>
<td>• Active connective tissue disease involving the skin (especially scleroderma and lupus)</td>
</tr>
<tr>
<td>• Tumors &gt; 5 cm (category 2B)</td>
</tr>
<tr>
<td>• Focally positive margin[^1]</td>
</tr>
<tr>
<td>• Women ≤ 35 y or premenopausal women with a known BRCA 1/2 mutation:</td>
</tr>
<tr>
<td>▶ Have an increased risk of ipsilateral breast recurrence or contralateral breast cancer with breast conserving therapy</td>
</tr>
<tr>
<td>▶ Prophylactic bilateral mastectomy for risk reduction may be considered.</td>
</tr>
</tbody>
</table>

[^1]: See Margin Status in Infiltrating Carcinoma (BINV-E).

---

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.
ADJUVANT HORMONAL THERAPY

Premenopausal

Tamoxifen\(^2\) for 2-3 y (category 1) ± ovarian suppression or ablation (category 2B)

Complete 5 y tamoxifen\(^2\) (category 1)

Postmenopausal

Exemestane or anastrozole to complete 5 y adjuvant hormonal therapy (category 2B)\(^3,4\)

Letrozole for 5 y (category 1)\(^3\)

Premenopausal

Anastrozole or letrozole for 5 y (category 1)\(^3\)

Complete 5 y tamoxifen\(^2\) (category 1)

Postmenopausal

Tamoxifen\(^2\) to 4.5-6 y

Letrozole for 5 y (category 1)\(^3\)

Women with contra-indication to aromatase inhibitors, who decline aromatase inhibitors or who are intolerant of the aromatase inhibitors, tamoxifen\(^2\) for 5 y (category 1)

1. See Definition of Menopause (BINV-I).
2. Some serotonin reuptake inhibitors decrease the formation of endoxifen, an active metabolite of tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. The clinical impact of these observations is not known.
3. The panel believes the three selective aromatase inhibitors (anastrozole, letrozole, exemestane) have similar antitumor efficacy and similar toxicity profiles. The aromatase inhibitor(s) specified is that used in the clinical trial(s) that most closely approximates the clinical situation. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.
4. This specific patient subset was not included in the trials of aromatase inhibitors given sequentially with adjuvant tamoxifen. Some women who appear to become postmenopausal on tamoxifen therapy have resumption of ovarian function after discontinuation of tamoxifen and initiation of an aromatase inhibitor. Therefore, serial monitoring of plasma estradiol and FSH levels is encouraged in this clinical setting. Should ovarian function resume, the aromatase inhibitor should be discontinued and tamoxifen resumed. See Definition of Menopause (BINV-I).

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.
ADJUVANT CHEMOTHERAPY 1,2,3,4,5

<table>
<thead>
<tr>
<th>NON-TRASTUZUMAB CONTAINING REGIMENS (all category 1)</th>
<th>TRASTUZUMAB CONTAINING REGIMENS (all category 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide) or</td>
<td>Preferred Adjuvant Regimen:</td>
</tr>
<tr>
<td>• FEC/CEF (cyclophosphamide/epirubicin/fluorouracil)</td>
<td>• AC → T + concurrent trastuzumab</td>
</tr>
<tr>
<td>• AC (doxorubicin/cyclophosphamide) ± sequential paclitaxel6</td>
<td>(doxorubicin/cyclophosphamide followed by paclitaxel plus</td>
</tr>
<tr>
<td>• EC (epirubicin/cyclophosphamide)</td>
<td>trastuzumab)</td>
</tr>
<tr>
<td>• TAC (doxorubicin/cyclophosphamide) with filgrastim support6</td>
<td>Other Adjuvant Regimens:</td>
</tr>
<tr>
<td>• A→ CMF7 (doxorubicin followed by cyclophosphamide/</td>
<td>• Docetaxel + trastuzumab → FEC</td>
</tr>
<tr>
<td>methotrexate/fluorouracil)</td>
<td>• TCH (docetaxel, carboplatin, trastuzumab)</td>
</tr>
<tr>
<td>• E→ CMF (epirubicin followed by</td>
<td>• Chemotherapy followed by trastuzumab sequentially9</td>
</tr>
<tr>
<td>cyclophosphamide/methotrexate/fluorouracil)</td>
<td>• AC → docetaxel + trastuzumab</td>
</tr>
<tr>
<td>• CMF (cyclophosphamide/methotrexate/fluorouracil)</td>
<td>Neoadjuvant:</td>
</tr>
<tr>
<td>• AC x 4 (dorxorubicin/cyclophosphamide) + sequential paclitaxel × 4,</td>
<td>• T + trastuzumab → CEF + trastuzumab</td>
</tr>
<tr>
<td>every 2 weekly regimen with filgrastim support8</td>
<td>(paclitaxel plus trastuzumab followed by</td>
</tr>
<tr>
<td>• A→ T→ C (doxorubicin followed by paclitaxel followed by</td>
<td>cyclophosphamide/epirubicin/fluorouracil plus trastuzumab)</td>
</tr>
<tr>
<td>cyclophosphamide) every 2 weekly regimen with filgrastim support8</td>
<td></td>
</tr>
<tr>
<td>• FEC → T (fluorouracil/epirubicin/cyclophosphamide followed by</td>
<td></td>
</tr>
<tr>
<td>docetaxel)</td>
<td></td>
</tr>
</tbody>
</table>

See Representative Adjuvant Chemotherapy Regimens on next page, BINV-H (2 of 5)

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

2In patients with HER2 positive and axillary lymph node positive breast cancer, trastuzumab should be incorporated into the adjuvant therapy. (category 1) Trastuzumab should also be considered for patients with lymph node negative tumors greater than or equal to 1 cm and are HER2 positive. (category 1) Trastuzumab may be given beginning either concurrent with paclitaxel as part of the AC followed by paclitaxel regimen, or alternatively after the completion of chemotherapy. Trastuzumab should not be given concurrent with an anthracycline because of cardiac toxicity. Trastuzumab should be given for one year, (with the exception of the docetaxel + trastuzumab → FEC regimen in which trastuzumab was given for 9 weeks), with cardiac monitoring, and by either the weekly or every three weekly schedule.

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

4Chemotherapy and tamoxifen used as adjuvant therapy should be given sequentially with tamoxifen following chemotherapy.

5For node-positive patients, anthracycline-containing chemotherapy regimens are preferred.

6Randomized clinical trials demonstrate that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.

7The data supporting A → CMF are limited to patients with four or more positive nodes.

8A single randomized clinical trial with 36 mo median follow-up demonstrated superior disease-free and overall survival with every two weekly treatment with AC x 4 sequential with paclitaxel x 4 or with A x 4 followed by T x 4, followed by C x 4 versus every 3 weekly treatment with the same regimens.


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.
Invasive Breast Cancer

REPRESENTATIVE ADJUVANT CHEMOTHERAPY REGIMENS FOR BREAST CANCER*

NON-TRASTUZUMAB COMBINATIONS

FAC chemotherapy
5-Fluorouracil 500 mg/m² IV days 1 & 8 or days 1 & 4
Doxorubicin 50 mg/m² IV day 1
Cyclophosphamide 500 mg/m² IV day 1
Cycled every 21 days for 6 cycles.

CAF chemotherapy
Cyclophosphamide 100 mg/m² PO days 1-14
Doxorubicin 30 mg/m² IV days 1 & 8
5-Fluorouracil 500 mg/m² IV days 1 & 8
Cycled every 28 days for 6 cycles.

FEC chemotherapy
Cyclophosphamide 75 mg/m² PO days 1-14
Epirubicin 60 mg/m² IV days 1 & 8
5-Fluorouracil 500 mg/m² IV days 1 & 8
With cotrimoxazole support.
Cycled every 28 days for 6 cycles.

AC chemotherapy
Doxorubicin 60 mg/m² IV day 1
Cyclophosphamide 600 mg/m² IV day 1
Cycled every 21 days for 4 cycles.

E followed by CMF chemotherapy
Epirubicin 100 mg/m² IV day 1
Cycled every 21 days for 4 cycles.
Followed by
Cyclophosphamide 100 mg/m² PO days 1-14
Methotrexate 40 mg/m² IV days 1 & 8
5-Fluorouracil 600 mg/m² IV days 1 & 8
Cycled every 28 days for 4 cycles.

EC chemotherapy
Epirubicin 100 mg/m² IV day 1
Cyclophosphamide 830 mg/m² IV day 1
Cycled every 21 days for 8 cycles.

TAC chemotherapy
Docetaxel 75 mg/m² IV day 1
Doxorubicin 50 mg/m² IV day 1
Cyclophosphamide 500 mg/m² IV day 1
Cycled every 21 days for 6 cycles.
(All cycles are with filgrastim support).

A followed by CMF chemotherapy
Doxorubicin 75 mg/m² IV day 1
Cycled every 21 days for 4 cycles.
Followed by
Cyclophosphamide 600 mg/m² IV day 1
Methotrexate 40 mg/m² IV day 1
5-Fluorouracil 600 mg/m² IV day 1
Cycled every 21 days for 8 cycles.

TAC chemotherapy
Docetaxel 75 mg/m² IV day 1
Doxorubicin 50 mg/m² IV day 1
Cyclophosphamide 500 mg/m² IV day 1
Cycled every 21 days for 6 cycles.
(All cycles are with filgrastim support).

A followed by CMF chemotherapy
Doxorubicin 60 mg/m² IV day 1
Cycled every 21 days for 4 cycles.
Followed by
Cyclophosphamide 600 mg/m² IV day 1
Methotrexate 40 mg/m² IV day 1
5-Fluorouracil 600 mg/m² IV day 1
Cycled every 21 days for 8 cycles.

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

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.
## REPRESENTATIVE ADJUVANT CHEMOTHERAPY REGIMENS FOR BREAST CANCER*

### NON-TRASTUZUMAB COMBINATIONS

- **Dose-dense A-T-C chemotherapy**
  - Doxorubicin 60 mg/m² IV day 1
  - Cycled every 14 days for 4 cycles. Followed by
  - Paclitaxel 175 mg/m² by 3 h IV day 1
  - Cycled every 14 days for 4 cycles. Followed by
  - Cyclophosphamide 600 mg/m² IV day 1
  - Cycled every 14 days for 4 cycles. (All cycles are with filgrastim support).

- **FEC followed by docetaxel chemotherapy**
  - 5-Fluorouracil 500 mg/m² IV day 1
  - Epirubicin 100 mg/m² IV day 1
  - Cyclophosphamide 500 mg/m² day 1
  - Cycled every 21 days for 3 cycles. Followed by
  - Docetaxel 100 mg/m² day 1
  - Cycled every 21 days for 3 cycles.

### TRASTUZUMAB CONTAINING COMBINATIONS

- **AC followed by T chemotherapy with Trastuzumab**
  - Doxorubicin 60 mg/m² IV day 1
  - Cyclophosphamide 600 mg/m² IV day 1
  - Cycled every 21 days for 4 cycles. Followed by
  - Paclitaxel 175 mg/m² by 3 h IV day 1
  - Cycled every 21 days for 4 cycles. OR
  - Paclitaxel 80 mg/m² by 1 h IV weekly for 12 wks
  - Trastuzumab 4 mg/kg IV with first dose of paclitaxel
  - Trastuzumab 2 mg/kg IV weekly to complete 1 year of treatment. As an alternative, trastuzumab 6 mg/kg IV every 3 wk may be used following the completion of paclitaxel, and given to complete 1y of trastuzumab treatment.

- **Docetaxel + trastuzumab followed by FEC**
  - Docetaxel 100 mg/m² by 1 h IV day 1
  - Cycled every 21 days for 3 cycles. With
  - Trastuzumab 4 mg/kg IV with first dose of docetaxel day 1
  - Followed by
  - Trastuzumab 2 mg/kg IV weekly to complete 9 weeks of trastuzumab.
  - Followed by
  - 5-Fluorouracil 600 mg/m² IV day 1
  - Epirubicin 60 mg/m² day 1
  - Cyclophosphamide 600 mg/m² day 1
  - Cycled every 21 days for 3 cycles. Cardiac monitoring at baseline, after last FEC cycle, at 12 and 36 mo after chemotherapy.

- **TCH (docetaxel, carboplatin, trastuzumab)**
  - Docetaxel 75 mg/m² IV day 1
  - Followed by
  - Carboplatin AUC 6 IV day 1
  - Cycled every 21 days for 6 cycles. With
  - Trastuzumab 4 mg/kg week 1
  - Trastuzumab 2 mg/kg for 17 weeks
  - Followed by
  - Trastuzumab 6 mg/kg IV every 3 weeks to complete 1 year of trastuzumab therapy.

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

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

---

**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.
Neoadjuvant T followed by FEC chemotherapy with trastuzumab

- Trastuzumab 4 mg/kg IV for one dose beginning just prior to first dose of paclitaxel
- Trastuzumab 2 mg/kg IV weekly for 23 wks
- Paclitaxel 225 mg/m² by 24 h IV infusion every 21 days for 4 cycles

Chemotherapy followed by trastuzumab

- Approved adjuvant chemotherapy regimen for at least 4 cycles
- Trastuzumab 8 mg/kg IV times 1 dose
- Trastuzumab 6 mg/kg IV every 21 days for 1 y
- Cardiac monitoring at baseline, 3, 6, and 9 mo.

AC followed by docetaxel with trastuzumab

- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² day 1
- Cycled every 21 days for 4 cycles
- Docetaxel 100 mg/m²
- Cycled every 21 days for 4 cycles
- With Trastuzumab 4 mg/kg IV week one
- Trastuzumab 2 mg/kg IV weekly for 11 weeks
- Trastuzumab 6 mg/kg every 21 days to complete 1 y of trastuzumab therapy
- Cardiac monitoring at baseline, 3, 6, and 9 mo.

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.
REFERENCES FOR REPRESENTATIVE ADJUVANT CHEMOTHERAPY REGIMENS FOR BREAST CANCER


7. Mamounas EP, Bryant J, Lembersky BC, et al: Paclitaxel (T) following doxorubicin/cyclophosphamide (AC) as adjuvant chemotherapy for node-positive breast cancer:


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.
DEFINITION OF MENOPAUSE

Clinical trials in breast cancer have utilized a variety of definitions of menopause. Menopause is generally the permanent cessation of menses, and as the term is utilized in breast cancer management includes a profound and permanent decrease in ovarian estrogen synthesis. Reasonable criteria for determining menopause include any of the following:

- Prior bilateral oophorectomy
- Age ≥ 60 y
- Age < 60 y and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and FSH and estradiol in the postmenopausal range
- If taking tamoxifen or toremifene, and age < 60 y, then FSH and plasma estradiol level in postmenopausal ranges

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

(For first-line hormonal therapy see BINV-16)

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

<table>
<thead>
<tr>
<th>Postmenopausal Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Non-steroidal aromatase inhibitor (anastrozole, letrozole) or steroidal aromatase inactivator (exemestane)</td>
</tr>
<tr>
<td>- Fulvestrant</td>
</tr>
<tr>
<td>- Tamoxifen or Toremifene</td>
</tr>
<tr>
<td>- Megestrol acetate</td>
</tr>
<tr>
<td>- Fluoxymesterone</td>
</tr>
<tr>
<td>- Ethinyl estradiol</td>
</tr>
</tbody>
</table>

**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.
### Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer

**Preferred Single Agents**

- Doxorubicin
- Epirubicin
- Pegylated liposomal doxorubicin
- Paclitaxel
- Docetaxel
- Capecitabine
- Vinorelbine
- Gemcitabine
- Albumin-bound paclitaxel

**Preferred Combinations**

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

**Prefered Agents with Bevacizumab**

- Paclitaxel

**Other Active Agents**

- Cisplatin
- Carboplatin
- Etoposide (po)
- Vinblastine
- Fluorouracil continuous infusion

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**Preferred Chemotherapy Regimens for Use in Combination with Trastuzumab**

(HER2 positive metastatic disease)

- Paclitaxel ± Carboplatin
- Docetaxel
- Vinorelbine

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

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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.
REPRESENTATIVE CHEMOTHERAPY REGIMENS FOR METASTATIC BREAST CANCER* (Page 2 of 6)

COMBINATIONS

CAF chemotherapy\(^1\)
- Cyclophosphamide 100 mg/m\(^2\) PO days 1-14
- Doxorubicin 30 mg/m\(^2\) IV days 1 & 8
- 5-Fluorouracil 500 mg/m\(^2\) IV days 1 & 8
Cycled every 28 days.

FAC chemotherapy\(^2\)
- 5-Fluorouracil 500 mg/m\(^2\) IV days 1 & 8 or days 1 & 4
- Doxorubicin 50 mg/m\(^2\) IV day 1
- Cyclophosphamide 500 mg/m\(^2\) IV day 1
Cycled every 21 days.

AC chemotherapy\(^3\)
- Doxorubicin 60 mg/m\(^2\) IV day 1
- Cyclophosphamide 600 mg/m\(^2\) IV day 1
Cycled every 21 days.

CMF chemotherapy\(^4\)
- Cyclophosphamide 100 mg/m\(^2\) PO days 1-14
- Methotrexate 40 mg/m\(^2\) IV days 1 & 8
- 5-Fluorouracil 600 mg/m\(^2\) IV days 1 & 8
Cycled every 28 days.

Docetaxel and Capecitabine\(^5\)
- Docetaxel 75 mg/m\(^2\) IV day 1
- Capecitabine 950 mg/m\(^2\) PO twice daily days 1-14
Cycled every 21 days.

GT Chemotherapy\(^6\)
- Paclitaxel 175 mg/m\(^2\) IV by 3 h IV infusion day 1
- Gemcitabine 1250 mg/m\(^2\) IV days 1 & 8 (following paclitaxel on day 1)
Cycled every 21 days.

FEC chemotherapy\(^7\)
- Cyclophosphamide 400 mg/m\(^2\) IV days 1 & 8
- Epirubicin 50 mg/m\(^2\) IV days 1 & 8
- 5-Fluorouracil 500 mg/m\(^2\) IV days 1 & 8
Cycled every 28 days.

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

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.
SINGLE AGENTS

- Doxorubicin\(^8\) 60-75 mg/m\(^2\) IV day 1, cycled every 21 days
  OR
- Doxorubicin 20 mg/m\(^2\) IV, weekly.

- Epirubicin\(^9\) 60-90 mg/m\(^2\) IV day 1
  Cycled every 21 days.

- Pegylated liposomal encapsulated doxorubicin\(^10\) 50 mg/m\(^2\) IV day 1
  Cycled every 28 days.

- Paclitaxel 175 mg/m\(^2\) by 3 h IV infusion day 1
  Cycled every 21 days.\(^{11}\)
  OR
- Paclitaxel 80 mg/m\(^2\) by 1 h IV infusion weekly.\(^{12}\)

- Docetaxel 60-100 mg/m\(^2\) by 1 h IV infusion day 1
  Cycled every 21 days.\(^{13,14}\)
  OR
- Docetaxel 40 mg/m\(^2\) by 1 h IV infusion weekly for 6 wks followed by
  a 2 week rest, then repeated.\(^{15}\)

  Vinorelbine 25 mg/m\(^2\) IV weekly\(^{16}\)

  Capecitabine 1000-1250 mg/m\(^2\) PO twice daily days 1-14
  Cycled every 21 days.

  Gemcitabine 800-1200 mg/m\(^2\) IV days 1, 8 & 15
  Cycled every 28 days.\(^{17}\)

- Albumin-bound paclitaxel 260 mg/m\(^2\) by 30 minute IV infusion
  Cycled every 21 days.\(^{18}\)

BEVACIZUMAB CONTAINING REGIMENS

- Paclitaxel plus bevacizumab\(^19\)
  - Paclitaxel 90 mg/m\(^2\) by 1 h IV days 1, 8 & 15
  - Bevacizumab 10 mg/kg IV days 1 & 15
  Cycled every 28 days.

\(^{18}\)The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.
### REPRESENTATIVE CHEMOTHERAPY REGIMENS FOR METASTATIC BREAST CANCER IN COMBINATION WITH TRASTUZUMAB*

<table>
<thead>
<tr>
<th>CHEMOTHERAPY COMPONENT</th>
<th>TRASTUZUMAB COMPONENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COMBINATIONS</strong></td>
<td><strong>Trastuzumab 4 mg/kg IV by 90 min infusion day 1</strong>&lt;br&gt;Followed by <strong>2 mg/kg IV by 30 min infusion weekly</strong>&lt;sup&gt;22,26&lt;/sup&gt; OR <strong>Trastuzumab 8 mg/kg IV by 90 min infusion day 1</strong>&lt;br&gt;Followed by <strong>6 mg/kg IV by 90 min infusion every 3 weeks</strong>&lt;sup&gt;27&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>PCH</strong>&lt;sup&gt;20&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>• Carboplatin AUC of 6 IV day 1</td>
<td></td>
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<tr>
<td>• Paclitaxel 175 mg/m² by 3 h IV infusion day 1</td>
<td></td>
</tr>
<tr>
<td>Cycled every 21 days.</td>
<td></td>
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<tr>
<td><strong>Weekly TCH</strong>&lt;sup&gt;21&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>• Paclitaxel 80 mg/m² by 1 h IV infusion days 1, 8 &amp; 15</td>
<td></td>
</tr>
<tr>
<td>• Carboplatin AUC of 2 IV days 1, 8 &amp; 15</td>
<td></td>
</tr>
<tr>
<td>Cycled every 28 days.</td>
<td></td>
</tr>
<tr>
<td><strong>SINGLE AGENTS</strong></td>
<td></td>
</tr>
<tr>
<td>• Paclitaxel 175 mg/m² by 3 h IV infusion day 1</td>
<td></td>
</tr>
<tr>
<td>Cycled every 21 days.&lt;sup&gt;22&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>• Paclitaxel 80-90 mg/m² by 1 h IV infusion weekly&lt;sup&gt;23&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Docetaxel 80 to 100 mg/m² by 30 min IV infusion day 1</strong>&lt;br&gt;Cycled every 21 days</td>
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<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>• Docetaxel 35 mg/m² by 30 min IV infusion weekly&lt;sup&gt;24&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>• Vinorelbine 25 mg/m² IV weekly&lt;sup&gt;15,25&lt;/sup&gt;</td>
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</table>

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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.*
REFERENCES FOR REPRESENTATIVE CHEMOTHERAPY REGIMENS FOR METASTATIC BREAST CANCER and in COMBINATION WITH TRASTUZUMAB*


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.
REFERENCES FOR REPRESENTATIVE CHEMOTHERAPY REGIMENS FOR
METASTATIC BREAST CANCER and in COMBINATION WITH TRASTUZUMAB*

13Burris HAR: Single-agent docetaxel (Taxotere) in randomized phase III trials. Semin Oncol. 26:1-6, 1999
17Seidman AD: Gemcitabine as single-agent therapy in the management of advanced breast cancer. Oncology (Huntingt) 15(Suppl 3):11-14, 2001

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.
**Phyllodes Tumor**

**Clinical Presentation**
- Palpable mass
- Rapid growth
- Large size (> 2 cm)
- Imaging with ultrasound suggestive of fibroadenoma except for size and/or history of growth

**Workup**
- History and physical exam
- Ultrasound
- Mammogram for women ≥ 30 y

**Findings**
- Fibroadenoma → Observe
- Phyllodes tumor → Wide excisionc without axillary staging
- Invasive or in situ cancer → See appropriate guideline
- Fibroadenoma or indeterminate → Excisional biopsyb → Observe
- Core needle biopsya
- Phyllodes tumor → Wide excisionc without axillary staging
- Invasive or in situ cancer → See appropriate guideline

**Treatment**
- Observe

---

*a* FNA will not, and core biopsy may not distinguish fibroadenoma from phyllodes tumor in most cases.

*b* Excisional biopsy includes complete mass removal, but without the intent of obtaining surgical margins.

*c* Wide excision means excision with the intention of obtaining surgical margins ≥ 1 cm. Narrow surgical margins are associated with heightened local recurrence risk, but are not an absolute indication for mastectomy when partial mastectomy fails to achieve margin width ≥ 1 cm.

---

**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.
## Phyllodes Tumor

### PHYLLODES TUMOR RECURRENCE

<table>
<thead>
<tr>
<th>CLINICAL PRESENTATION</th>
<th>WORKUP</th>
<th>FINDINGS</th>
<th>TREATMENT</th>
</tr>
</thead>
</table>
| Locally recurrent breast mass following excision of phyllodes tumor | • History and physical exam  
• Ultrasound  
• Mammogram  
• Tissue sampling (histology preferred)  
• Consider chest imaging | No metastatic disease  
Metastatic disease | Re-excision with wide margins without axillary staging  
Consider post-operative radiation (category 3)\(^d\)  
Consider surgery/radiation therapy for local control (category 3) |

\(^d\)There is no prospective randomized data supporting the use of radiation treatment with phyllodes tumors. However, in the setting where additional recurrence would create significant morbidity, eg, chest wall recurrence following salvage mastectomy, radiation therapy may be considered, following the same principles that are applied to the treatment of soft tissue sarcoma.

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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.
Clinical suspicion of Paget's disease

- Clinical breast exam
- Diagnostic bilateral mammogram, ultrasound as necessary
- Breast MRI (optional)

Examination or imaging positive for breast lesion

Examination and imaging negative for breast lesion

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.

a Nipple or areolar eczema, ulceration, bleeding, itching.
b See Principles of Dedicated Breast MRI Testing (BINV-B).
Paget’s Disease

**WORKUP**

**Examination or imaging positive for breast lesion**
- Core biopsy of breast lesion and full thickness skin biopsy of involved nipple-areola complex (NAC)
- Breast and NAC biopsy negative
  - Clinical follow-up
  - Re-biopsy if not healing
- Breast DCIS and NAC Paget’s
  - Mastectomy ± axillary staging
  - or
  - Excision of breast tumor and excision NAC with whole breast radiation, consider boost to breast and NAC sites
- Breast invasive cancer and NAC Paget’s
  - Mastectomy ± axillary staging (See BINV-C)
  - or
  - Excision of breast tumor and excision NAC + axillary staging (See BINV-C) with whole breast radiation, consider boost to breast and NAC sites
- Breast negative for cancer and positive NAC Paget’s
  - Mastectomy + axillary staging (See BINV-C)
  - or
  - Excision of NAC with whole breast radiation, consider boost to NAC sites

**Examination and imaging negative for breast lesion**
- • Consider MRI if not previously done
  - • Full thickness skin biopsy of involved NAC
  - NAC biopsy positive for Paget’s
    - Mastectomy + axillary staging (See BINV-C)
    - or
    - Excision of NAC with whole breast radiation, consider boost to NAC sites
  - NAC biopsy negative for Paget’s
    - Clinical follow-up
    - Re-biopsy if not healing

---

**TREATMENT**

- Breast and NAC biopsy negative
  - Clinical follow-up
  - Re-biopsy if not healing
- Breast DCIS and NAC Paget’s
  - Mastectomy ± axillary staging
  - or
  - Excision of breast tumor and excision NAC with whole breast radiation, consider boost to breast and NAC sites
- Breast invasive cancer and NAC Paget’s
  - Mastectomy ± axillary staging (See BINV-C)
  - or
  - Excision of breast tumor and excision NAC + axillary staging (See BINV-C) with whole breast radiation, consider boost to breast and NAC sites
- Breast negative for cancer and positive NAC Paget’s
  - Mastectomy + axillary staging (See BINV-C)
  - or
  - Excision of NAC with whole breast radiation, consider boost to NAC sites

---

**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.

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CLINICAL PRESENTATION

Pregnant patient with confirmed breast cancer diagnosis
No distant metastases on staging

1st trimester
Discuss termination: Non-therapeutic
Continuing pregnancy
Mastectomy + axillary staging

2nd trimester/Early 3rd trimester
Mastectomy or breast-conserving surgery + axillary staging
or
Neoadjuvant chemotherapy, mastectomy or breast-conserving surgery + axillary staging post-partum

Late 3rd trimester
Mastectomy or breast-conserving surgery + axillary staging

PRIMARY TREATMENT

ADJUVANT TREATMENT

Begin adjuvant chemotherapy in 2nd trimester
± Adjuvant radiation therapy post-partum
± Adjuvant endocrine therapy post-partum

Adjuvant chemotherapy
± Adjuvant radiation therapy post-partum
± Adjuvant endocrine therapy post-partum

± Adjuvant radiation therapy post-partum
± Adjuvant endocrine therapy post-partum

± Adjuvant radiation therapy post-partum
± Adjuvant endocrine therapy post-partum

± Adjuvant radiation therapy post-partum
± Adjuvant endocrine therapy post-partum

a Considerations and selection of optimal local therapy and systemic therapy are similar to that recommended in non-pregnancy associated breast cancer, see other sections of this guideline. Chemotherapy should not be administered during the first trimester of pregnancy and radiation therapy should not be administered during any trimester of pregnancy. Most experience with chemotherapy during pregnancy for breast cancer is from regimens that utilize various combinations of doxorubicin, cyclophosphamide and fluorouracil. Consideration for post-partum chemotherapy are the same as for non-pregnancy associated breast cancer.
b See Surgical Axillary Lymph Node Staging (BINV-C).
c Due to limited data the use of isosulfan blue is not recommended in pregnant patients.

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.
### Staging

#### Table 1

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

**Primary Tumor (T)**  
Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. If the measurement is made by the physical examination, the examiner will use the major headings (T1, T2, or T3). If other measurements, such as mammographic or pathologic measurements, are used, the subsets of T1 can be used. Tumors should be measured to the nearest 0.1 cm increment.

<table>
<thead>
<tr>
<th>T</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>Tis (DCIS)</td>
<td>Ductal carcinoma in situ</td>
</tr>
<tr>
<td>Tis (LCIS)</td>
<td>Lobular carcinoma in situ</td>
</tr>
<tr>
<td>Tis (Paget's)</td>
<td>Paget's disease of the nipple with no tumor</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>T1</th>
<th>Tumor 2 cm or less in greatest dimension</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1mic</td>
<td>Microinvasion 0.1 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor more than 0.5 cm but not more than 1 cm in greatest dimension</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor more than 1 cm but not more than 2 cm in greatest dimension</td>
</tr>
</tbody>
</table>

| 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, not including pectoralis muscle               |

| 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                                                  |

**Regional Lymph Nodes (N)**

**Clinical**

<table>
<thead>
<tr>
<th>N</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed (e.g., previously removed)</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis to movable ipsilateral axillary lymph node(s)</td>
</tr>
<tr>
<td>N2</td>
<td>Metastases in ipsilateral axillary lymph nodes fixed or matted, or in * clinically apparent* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastases in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis only in * clinically apparent* ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in * clinically apparent* ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement</td>
</tr>
<tr>
<td>N3a</td>
<td>Metastasis in ipsilateral infraclavicular lymph node(s)</td>
</tr>
<tr>
<td>N3b</td>
<td>Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)</td>
</tr>
<tr>
<td>N3c</td>
<td>Metastasis in ipsilateral supraclavicular lymph node(s)</td>
</tr>
</tbody>
</table>

*Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.

Staging continued on next page (ST-2)
### Table 1 (continued)

<table>
<thead>
<tr>
<th>Pathologic (pN)*</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pNX</strong></td>
<td>Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)</td>
</tr>
<tr>
<td><strong>pN0</strong></td>
<td>No regional lymph node metastasis histologically, no additional examination for isolated tumor cells (ITC)</td>
</tr>
<tr>
<td><strong>pN0(i-)</strong></td>
<td>No regional lymph node metastasis histologically, negative IHC</td>
</tr>
<tr>
<td><strong>pN0(i+)</strong></td>
<td>No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm</td>
</tr>
<tr>
<td><strong>pN0(mol-)</strong></td>
<td>No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)*</td>
</tr>
<tr>
<td><strong>pN0(mol+)</strong></td>
<td>No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)*</td>
</tr>
</tbody>
</table>

*Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary node dissection is designated (sn) for “sentinel node,” e.g., pN0(i+) (sn).

b RT-PCR: reverse transcriptase/polymerase chain reaction.

| pN1 | Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent** |
| **pN1mi** | Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm) |
| **pN1a** | Metastasis in 1 to 3 axillary lymph nodes |
| **pN1b** | Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent** |

| pN2 | Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis |
| **pN2a** | Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm) |
| **pN2b** | Metastasis in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis |

| pN3 | Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes |
| **pN3a** | Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastasis to the infraclavicular lymph nodes |
| **pN3b** | Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent** |
| **pN3c** | Metastasis in ipsilateral supraclavicular lymph nodes |

* Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

** Not clinically apparent is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

Staging continued on next page (ST-3)
**Table 1 (continued)**

<table>
<thead>
<tr>
<th>Distant Metastasis (M)</th>
<th>Stage IIA</th>
<th>Stage IIIB</th>
<th>Stage IIIA</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>T0 N1 M0</td>
<td>T4 N0 M0</td>
<td>T0 N2 M0</td>
<td>Any T Any N M1</td>
</tr>
<tr>
<td>M0</td>
<td>T1* N1 M0</td>
<td>T4 N1 M0</td>
<td>T2 N2 M0</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>T2 N0 M0</td>
<td>T4 N2 M0</td>
<td>T3 N1 M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3 N0 M0</td>
<td>T4 N3 M0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**STAGE GROUPING**

- Stage 0: Tis N0 M0
- Stage I: T1* N0 M0
- Stage IIA: T0 N1 M0, T1* N1 M0
- Stage IIB: T2 N1 M0
- Stage IIIA: T0 N2 M0, T1* N2 M0
- Stage IIIB: T4 N0 M0, T4 N1 M0, T4 N2 M0
- Stage IV: Any T Any N M1

Note: Stage designation may be changed if post-surgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.

**HISTOPATHOLOGIC TYPE**

- In situ Carcinomas
  - NOS (not otherwise specified)
  - Intraductal
  - Paget’s disease and intraductal
- Invasive Carcinomas
  - NOS
  - Ductal
  - Inflammatory
  - Medullary, NOS
  - Medullary with lymphoid stroma
  - Mucinous
  - Papillary (predominantly micropapillary pattern)
  - Tubular
  - Lobular
  - Paget’s disease and infiltrating
  - Undifferentiated
  - Squamous cell
  - Adenoid cystic
  - Secretory
  - Cribriform

**HISTOPATHOLOGIC GRADE (G)**

All invasive breast carcinomas with the exception of medullary carcinoma should be graded. The Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system) is recommended.\(^1\) The grade for a tumor is determined by assessing morphologic features (tubule formation, nuclear pleomorphism, and mitotic count), assigning a value of 1 (favorable) to 3 (unfavorable) for each feature, and adding together the scores for all three categories. A combined score of 3-5 points is grade 1; a combined score of 6-7 points is grade 2; a combined score of 8-9 points is grade 3.


**HISTOLOGIC GRADE (NOTTINGHAM COMBINED HISTOLOGIC GRADE IS RECOMMENDED)**

- GX: Grade cannot be assessed
- G1: Low combined histologic grade (favorable)
- G2: Intermediate combined histologic grade (moderately favorable)
- G3: High combined histologic grade (unfavorable)

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer-Verlag New York, Inc., on behalf of the AJCC.
Overview

The American Cancer Society estimates that 214,640 new cases of breast cancer will be diagnosed and 41,430 will die of breast cancer in the United States in 2006. Breast cancer is the most common malignancy in women in the United States and is second only to lung cancer as a cause of cancer death.

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

The etiology of the vast majority of breast cancer cases is unknown. However, numerous risk factors for the disease have been established. These risk factors include: female gender; increasing patient age; family history of breast cancer at a young age; early menarche; late menopause; older age at first live childbirth; prolonged hormone replacement therapy; previous exposure to therapeutic chest wall irradiation; benign proliferative breast disease; and genetic mutations such as the BRCA1/2 genes. However, except for female gender and increasing patient 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 Genetic/Familial High-Risk Assessment Guidelines. Women at increased risk for breast cancer (generally those with a greater than 1.67% 5-year risk of breast cancer using the Gail model of risk assessment) may consider risk reduction strategies (see NCCN Breast Cancer Risk Reduction Guidelines).

Staging

Effective January 2003, the American Joint Committee on Cancer (AJCC) implemented a revision of the Cancer Staging Manual (sixth edition) containing important changes and additions in the TNM staging system for breast cancer (Table 1). This revision differs from the 1997 edition of the AJCC staging by incorporating the increasing use of novel imaging and pathology techniques employed at diagnosis (eg, sentinel node biopsy and immunohistochemistry [IHC] evaluation of nodes) and the number of lymph nodes involved as a factor in staging allocation.
The most substantial changes are:

1. Micrometastases to ipsilateral axillary lymph nodes are distinguished from isolated tumor cells on the basis of size and histological evidence of malignant activity. All metastatic lesions to ipsilateral axillary lymph nodes no larger than 0.2 mm, whether detected by hematoxylin and eosin (H&E) staining or IHC, will be described as pN0(i+). pN0(i-) is used to indicate no detectable tumor cells by either H&E or IHC. The designation pN1mi with no additional identifiers will be used for micrometastases greater than 0.2 mm but no greater than 2.0 mm in greatest dimension. These identifiers will be used for micrometastases greater than 0.2 mm but no greater than 2.0 mm in greatest dimension.7

2. Identifiers are added to indicate the use of sentinel lymph node resection and IHC or molecular pathology techniques.

3. The number of involved nodes as determined by routine H&E staining (preferred method) or by IHC staining impacts pathologic N staging (pN1 if 1 to 3 lymph nodes, pN2 if 4 to 9 lymph nodes, and pN3 if 10 or more lymph nodes are involved).

4. Metastases to infraclavicular nodes are categorized as N3 disease.

5. Metastases to internal mammary (IM) nodes impact staging according to the method of detection and presence or absence of concomitant axillary lymph node involvement (N1 disease if involved IM lymph nodes are detected exclusively using sentinel lymph node detection procedure; N2 disease if detected using any other imaging study or clinical examination; or N3 disease if concomitant axillary lymph node involvement is present).

6. Metastasis to ipsilateral supraclavicular lymph nodes is no longer considered M1 disease and is classified as N3 disease.

Although determination of the specific TNM status has become more complex (especially with regard to lymph node staging), the allocation of specific TNM combinations to different stage groupings remains the same, with the exception of the creation of stage IIIIC to specifically identify patients with TanyN3M0 disease. This revised staging system recognizes the heterogeneity of breast cancer and the need to create uniform data collection standards to better assess both the long-term outcome of specific patient subgroups and the impact of novel imaging or pathology techniques.8

Pathology Assessment

A central component of the treatment of breast cancer is full knowledge of extent of disease and biologic features. These factors contribute to the determination of the stage of disease, assist in the estimation of the risk that the cancer will recur, and provide information that predicts response to therapy (eg, hormone receptors and human epidermal growth factor receptor 2 [HER2]). These factors are determined by examination of excised tissue and provided in a written pathology report. Accurate pathology reporting requires communication between the clinician and the pathologist relating to relevant patient history, prior breast biopsies, prior irradiation to the chest, pregnancy status, characteristics of the abnormality biopsied (eg, palpable, mammographically detected, microcalcifications), clinical state of lymph nodes, presence of inflammatory change or other skin abnormality, and any prior treatment administered (eg, chemotherapy or radiotherapy). The specimens should be oriented for the pathologist, and specific requests for determination of biomarkers should be stated (eg, estrogen receptor, progesterone receptor, and HER2 status). The use of consistent, unambiguous standards for reporting is strongly encouraged. Data from both national and local surveys show that as many as 50% of pathology reports for breast cancer are missing some elements critical to patient management.8,9 Significant omissions include failure to orient and report surgical margins, and failure to report tumor grade consistently.

The College of American Pathologists (CAP) has developed pathology reporting protocols to promote complete and standardized reporting of malignant specimens. CAP provides a protocol for each disease site
that includes cancer case summaries (checklists) along with background documentation. These checklists form the basis for a synoptic, standardized reporting of pathologic findings. The checklists are available without charge through the CAP website at www.cap.org.

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

**Treatment Approach**

Conceptually, the treatment of breast cancer includes the treatment of local disease with surgery, radiation therapy (RT), or both, and the treatment of systemic disease with cytotoxic chemotherapy, endocrine therapy, biologic therapy or combinations of these. The need for and selection of various local or systemic therapies are based on a number of prognostic and predictive factors. These factors include tumor histology, clinical and pathologic characteristics of the primary tumor, axillary node status, tumor hormone receptor content, tumor HER2 status, presence or absence of detectable metastatic disease, patient comorbid conditions, patient age, and menopausal status. Breast cancer does occur in men, and men with breast cancer should be treated similarly to postmenopausal women, except that the use of aromatase inhibitors is ineffective without concomitant suppression of testicular steroidogenesis.\(^\text{10,11}\) Patient preference is a major component of the decision-making process, especially in situations in which survival rates are equivalent among the available treatment options.

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

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

**Pure Noninvasive Carcinomas (Stage 0)**

Both LCIS and DCIS may be difficult to distinguish from atypical hyperplasia or from carcinomas with early invasion.\(^\text{12,13}\) Therefore, pathology review of all cases is recommended. Bilateral diagnostic mammography should be performed to identify the presence of multiple primary tumors and to estimate the extent of the noninvasive lesion.

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

**Lobular carcinoma in situ**

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).\(^\text{14}\) The histologies of the invasive carcinomas tend to be favorable, and deaths from second invasive cancers are unusual in appropriately monitored women.\(^\text{15}\) Bilateral
mastectomy, with or without reconstruction, can be considered in special circumstances such as in women with BRCA1/2 mutations or a strong family history of breast cancer, or in women with very high levels of anxiety.

The risk of an invasive breast cancer after a diagnosis of LCIS is equal in both breasts.\textsuperscript{16} If mastectomy is considered as a risk reduction strategy, then a bilateral procedure is required to optimally minimize risk. Women treated with bilateral mastectomy are appropriate candidates for breast reconstruction.

There is evidence to support the existence of histologically aggressive variants of LCIS (eg, pleomorphic LCIS) which may have a greater potential than classic LCIS to develop into invasive lobular carcinoma.\textsuperscript{17} However, outcome data regarding treatment of patients with pleomorphic LCIS are lacking, due, in part, to a paucity of histologic categorization of variants of LCIS. Therefore, recommendations on the treatment of pleomorphic LCIS as a distinct entity of LCIS have not been made by the Panel.

Women with LCIS, whether they undergo observation only or are treated with bilateral mastectomy, have an excellent prognosis. Recent data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial show that tamoxifen given for 5 years is associated with an approximately 56% reduction (hazard ratio 0.44; 95% CI 0.16-1.06) in the risk of developing invasive breast cancer among women with LCIS.\textsuperscript{18,19} Results from the NSABP Study of Tamoxifen and Raloxifene (STAR) trial have shown raloxifene to be as effective as tamoxifen in reducing the risk of invasive cancer in postmenopausal patients with LCIS.\textsuperscript{20} Therefore, the use of tamoxifen in premenopausal women or tamoxifen or raloxifene in postmenopausal women should be considered as a risk reduction strategy in women with LCIS who are followed with observation (category 1). (For recommendations on risk reduction, see also the NCCN Breast Cancer Risk Reduction Guidelines.)

Follow-up of patients with LCIS includes physical examinations every 6 to 12 months for 5 years and then annually. Annual diagnostic mammography is recommended in patients being followed with clinical observation.

**Ductal carcinoma in situ**

Patients with DCIS and evidence of widespread disease (ie, disease in 2 or more quadrants) on mammography or other imaging, physical examination, or biopsy require a total mastectomy without lymph node dissection. For the vast majority of patients with more limited disease and in whom negative margins are achieved with the initial excision or with re-excision, breast-conserving therapy or total mastectomy are appropriate treatment options. Although mastectomy provides maximum local control, the long-term, cause-specific survival with mastectomy appears to be equivalent to that with excision and whole breast irradiation.\textsuperscript{21-23} Women treated with mastectomy are appropriate candidates for breast reconstruction. Contraindications to breast-conserving therapy with radiation therapy are listed in the algorithm (see BINV-F).

Prospective randomized trials have shown that the addition of whole breast irradiation to a margin-free excision of pure DCIS decreases the rate of in-breast disease recurrence, but does not affect overall survival.\textsuperscript{23,24} Although some non-controlled evidence suggests that selected patients have a low risk of in breast recurrence with excision alone without breast irradiation,\textsuperscript{25,26} based on high-level evidence from randomized trials, the NCCN guideline recommends the use of radiation after local excision in all patients with DCIS 0.5 cm or greater in diameter. The use of whole breast radiation after breast-conserving surgery reduces the relative risk of a local failure by approximately one
The use of a radiation boost (by photons, brachytherapy, or electron beam) to the tumor bed is recommended to maximize local control, especially in patients 50 years of age or younger. Many factors, including patient age, tumor size, tumor grade, and margin width, impact recurrence risk. The definition of a negative margin has not been firmly established in DCIS. There appears to be a consensus that margins greater than 10 mm are adequate and margins less than 1 mm are inadequate, but no uniform consensus exists for margin status between these values. Results from a retrospective study of 445 patients with pure DCIS treated by excision alone indicated that margin width was the most important independent predictor of local recurrence, although the trend for decreasing local recurrence risk with increasing margin width was most apparent with margins less than 1 mm and greater than or equal to 6 mm. Further complicating the issue of margin width is the impact of the fibroglandular boundary – the pectoral fascia and the superficial skin where narrower tumor free margins may provide adequate local control. Finally, because the choice of local treatment does not impact disease-related survival, the individual patient’s acceptance of the potential for an increased risk of local recurrence must be considered.

Axillary dissection is not recommended for patients with pure DCIS. However, a small proportion of women with apparent pure DCIS on initial biopsy will be found to have invasive breast cancer at the time of the definitive surgical procedure and thus ultimately require axillary lymph node staging. In patients with apparent pure DCIS to be treated with mastectomy or with excision in an anatomic location (eg, tail of the breast), which could compromise the performance of a future sentinel lymph node procedure, a sentinel lymph node procedure may be considered. Limited evidence suggests that 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 RT;
2) Total mastectomy, with or without reconstruction;
3) Excision alone followed by clinical observation.

Patients with mammographically detectable DCIS who elect breast conservation therapy should undergo post-excision mammography of the involved breast and specimen radiography to ensure that all mammographically detectable disease has been excised. Alternatively, some Panel members believe that specimen radiographs are adequate documentation of complete excision if such radiographs show that the abnormality (the mass and/or microcalcifications) is clearly within the specimen. Clips are used by some NCCN institutions to demarcate the biopsy area because DCIS may be clinically occult and further surgery may be required, pending the margin status review by pathology.

DCIS falls between atypical ductal hyperplasia and invasive ductal carcinoma within the spectrum of breast proliferative abnormalities. The NSABP Breast Cancer Prevention Trial showed an 86% reduction in the occurrence of invasive breast cancer in patients with atypical ductal hyperplasia treated with tamoxifen. These data also showed that tamoxifen led to a substantial reduction in the risk of developing benign breast disease. The Early Breast Cancer Trialists’ overview analysis showed that, with 5 years of tamoxifen therapy, women with estrogen receptor- (ER) positive or receptor-unknown invasive tumors had a 52% reduction in the annual odds of recurrence of invasive breast cancer. Similarly, the NSABP B-24 trial found a benefit from tamoxifen for women with DCIS after treatment with breast conservation surgery (BCS) and RT. In that study, women with DCIS who were treated with breast-conserving therapy were randomized to receive placebo or
tamoxifen. The women treated with tamoxifen had a 5% absolute reduction in recurrence risk and a 37% reduction in relative risk. The women receiving tamoxifen had an 8.2% total incidence of breast cancer (4.1% invasive and 4.2% noninvasive) compared with a 13.4% incidence of breast cancer (7.2% invasive and 6.2% noninvasive) in the placebo-treated group at a median follow-up of 74 months. A retrospective analysis of estrogen receptor expression in NSABP B-24 suggests that increased levels of ER expression predict for tamoxifen benefit in terms of reduction of risk for the development of both ipsilateral and contralateral breast cancer following breast-conserving therapy.

Tamoxifen treatment, therefore, may be considered for women with DCIS treated with breast-conserving therapy, especially in those with ER-positive DCIS (category 1 for those undergoing BCS + 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) and, in those who received breast-conserving therapy, to reduce the risk of an ipsilateral in breast recurrence (adjuvant therapy).

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

Stage I, IIA, IIB, or T3N1M0 Invasive Breast Cancer
The recommended work-up and staging of invasive breast cancer includes history and physical exam, a complete blood cell count, platelet count, liver function tests, chest imaging, bilateral diagnostic mammography, and, if necessary, breast ultrasonography, tumor estrogen and progesterone receptor determinations, HER2 tumor status determination, and pathology review.

Use of MRI to evaluate women considering breast-conserving therapy is optional (category 2B) (see BINV-B). If MRI imaging of the breast is performed, it should be done with a dedicated breast coil, with consultation with the multidisciplinary treatment team, and by a breast imaging team capable of performing MRI-guided biopsy. The limitations of breast MRI include a high percentage of false-positive findings. MRI imaging of the breast, therefore, should generally be considered in the staging of breast cancer for patients whose breasts cannot be imaged adequately with mammography and ultrasound (eg, women with very dense breast tissue, women with positive axillary nodal status and occult primary tumor presumed to originate in the breast, or to evaluate the chest wall). Patients should not be denied the option of breast conservation therapy based upon MRI findings alone in the absence of tissue sampling.

Radionuclide bone scanning and abdominal imaging with CT, ultrasound, or MRI are indicated for patients with T3N1M0 disease, if the patient has signs or symptoms related to bone or abdomen, or an elevated alkaline phosphatase. In the remaining patients, bone scan (category 2B) and abdominal imaging (category 2B) are considered optional.

The determination of HER2 status for all newly diagnosed invasive breast cancers is recommended. HER2 status can be assessed by measuring the number of HER2 gene copies (fluorescence in situ hybridization [FISH]), or by a complementary method in which the number of HER2 cell surface receptors is evaluated (immunohistochemistry [IHC]). Only 4 methods currently have United States Food and Drug Administration approval for determining the HER2 status of breast cancer tumors. These methods include: 1) the IHC HercepTest® (DAKO, Glostrup, Denmark); 2) the IHC Pathway® HER2 test (Ventana Medical Systems, Tucson, AZ); 3) the INFORM® HER2 FISH test (Ventana Medical Systems); 4) and the PathVysion®
HER2 FISH test (Vysis, Downers Grove, IL), although modifications of these methods are currently in use in many anatomic pathology laboratories. The accuracy of HER2 assays used in clinical practice is a major concern, and results from several studies have shown that false-positive as well as false-negative HER2 test results are common. An NCCN Task Force has recently reviewed this topic and issued recommendations on HER2 testing in breast cancer which are summarized in the guideline (see BINV-A). The Panel considers either an IHC or FISH test as an acceptable method for making an initial determination of HER2 tumor status provided that the test method has been validated and shown to be at least 95% concordant with another validated method. Evidence for 95% concordance between the HER2 assay used and a validated complementary HER2 testing method is also required. Breast cancer tumors are classified as HER2-positive if they demonstrate HER2 gene amplification by a FISH method or are scored as 3+ by an IHC method. Strategies for evaluating tumors with borderline or indeterminate HER2 status (eg, FISH [Pathvysion®] scores of 1.8-2.2 HER2 genes/chromosome 17/cell, FISH [INFORM®] scores of greater than 4 to less than 6 HER2 genes/cell, or 2+ scores by IHC) are described in the guideline (see BINV-A). HER2 testing should be performed only in laboratories accredited to carry out such testing. Further, these laboratories should have standardized HER2 testing procedures in place, as well as programs to periodically evaluate the proficiency of personnel performing HER2 testing. HER2 test reports must provide information on site of tumor; specimen type; histologic type; fixation method and time; block examined; HER2 testing method used; results of ongoing validation and concordance studies of the HER2 testing methods used in that laboratory, as well as other laboratory quality assurance information. Clinicians should be familiar with the significance of these criteria when making clinical recommendations for an individual patient.

A determination of the HER2 status of the tumor is recommended for prognostic purposes for patients with node-negative breast cancer. HER2 tumor status also provides baseline predictive information used in selecting optimal adjuvant/neoadjuvant therapy and in the selection of therapy for recurrent or metastatic disease (category 1). For example, retrospective analyses have demonstrated that anthracycline-based adjuvant therapy is superior to non-anthracycline-based adjuvant chemotherapy in patients with HER2-positive tumors, and that the dose of doxorubicin may be important in the treatment of tumors that are HER2-positive. However, prospective evidence of the predictive utility of HER2 status in early-stage and metastatic breast cancer is currently available only for trastuzumab-containing therapies.

**Local-regional treatment**

A number of randomized trials document that mastectomy with axillary lymph node dissection or breast-conserving therapy with lumpectomy, axillary dissection, and whole breast irradiation (breast-conserving therapy) are medically equivalent primary treatment options in the majority of women with stage I and stage II breast cancers (category 1). When breast-conserving therapy with lumpectomy and radiation therapy is performed, the Panel finds the data inadequate to support the use of partial breast irradiation outside the confines of a high-quality, prospective clinical trial. The use of breast-conserving therapy is absolutely contraindicated for patients who have received previous moderate- or high-dose RT to the breast or chest wall, are pregnant and would require RT during pregnancy, have diffuse suspicious or malignant-appearing microcalcifications on mammography, have widespread disease that cannot be incorporated by local excision through a single incision with a satisfactory cosmetic result, or have a positive pathologic margin (see BINV-E; BINV-F). Patients with a pathologically positive margin may undergo re-excision(s) to achieve a negative pathologic margin. If the
margins remain positive after re-excision(s), then mastectomy is required for optimal local disease control. In order to adequately assess margins following lumpectomy, the Panel recommends that the surgical specimens be oriented, that the pathologist provide descriptions of the gross and microscopic margin status, and the distance, orientation, and type of tumor (invasive or DCIS) in relation to the closest margin.

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

Several studies of women with early-stage breast cancer treated with breast-conserving therapy have identified young age as a significant predictor of an increased likelihood of ipsilateral breast tumor recurrence. Risk factors, such as a family history of breast cancer or a genetic predisposition for breast cancer (eg, BRCA 1/2 or other mutation), are more likely to exist in the population of young women with breast cancer, thereby confounding the independent contributions of age and treatment to clinical outcome. Survival outcomes for young women with breast cancer receiving either breast-conserving therapy or mastectomy are similar. The Panel recommends that women with breast cancer who are less than 35 years or premenopausal and carriers of a known BRCA 1/2 mutation consider additional risk reduction strategies (see BINV-F; NCCN Breast Risk Reduction Guidelines and NCCN Genetic/Familial High-Risk Assessment Guidelines).

In a study of women with clinical stage I, estrogen receptor-positive breast cancer, who were 70 years of age or older at diagnosis, patients were randomized to receive lumpectomy with whole breast radiation or lumpectomy alone, both with tamoxifen for 5 years. Local-regional recurrence rates were 1% in the lumpectomy, radiation and tamoxifen arm, and 4% in the lumpectomy plus tamoxifen arm. There were no differences in overall survival, disease-free survival or need for mastectomy. Similar results were obtained in another study of similar design. The Guidelines allow for the use of breast-conserving surgery (pathologically negative margin required) plus tamoxifen or an aromatase inhibitor without breast irradiation in women age 70 or older with clinically negative lymph nodes and ER positive breast cancer (category 1 with tamoxifen; category 2A with an aromatase inhibitor).

If adjuvant chemotherapy is indicated following breast-conserving surgery, RT should typically be given after chemotherapy is completed. Breast-conserving RT may be given concurrent with CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy, but methotrexate should either be withheld during the radiation or limited to no more than 2 doses concurrent with the radiation. Concurrent CMF chemotherapy with RT has been demonstrated to decrease the cosmetic outcome of breast-conserving therapy in some, but not all studies. The guideline includes a recommendation for regional lymph node RT in patients treated with breast-conserving surgery (see BINV-2) analogous to that recommended in patients treated with post-mastectomy regional lymph node irradiation (see BINV-3; subsequent discussion).

The NCCN Breast Cancer Treatment Guidelines include a guideline for surgical staging of the axilla for stages I, IIA, and IIB breast cancer (see BINV-C). A typical woman with clinical stage I or stage II breast cancer requires pathologic assessment of the axillary lymph node status.

Performance of sentinel lymph node mapping and resection in the surgical staging of the axilla is recommended by the Panel as the preferred method to assess the pathologic status of the axillary lymph nodes for patients with stage I or stage II breast cancer (see BINV-C). This recommendation is supported by results of recent studies.
randomized clinical trials showing decreased arm and shoulder morbidity (eg, pain, lymphedema, and sensory loss) in patients with breast cancer undergoing sentinel lymph node biopsy compared with patients undergoing standard axillary node dissection.\cite{84,86} No significant differences in the effectiveness of the sentinel lymph node procedure or level I and II dissection in determining the presence or absence of metastases in axillary nodes were seen in these studies. However, not all women are candidates for sentinel lymph node resection. The availability of an experienced sentinel lymph node team is mandatory for the use of sentinel lymph node mapping and excision.\cite{87,88} Women who have clinical stage I or II disease and do not have immediate access to an experienced sentinel node team should be considered for referral to an experienced sentinel lymph node team for the definitive surgical treatment of the breast and surgical axillary lymph node staging. In addition, potential candidates for sentinel lymph node mapping and excision should have clinically negative axillary lymph nodes, or a negative core or fine needle aspiration (FNA) biopsy of any clinically suspicious axillary lymph node(s). If the sentinel lymph node cannot be identified or is positive for metastasis, a formal axillary lymph node dissection should be performed (category 2A) or axillary RT administered (category 2B). 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 metastases by both H&E staining and cytokeratin IHC. The clinical significance of a lymph node that is negative by H&E staining but positive by cytokeratin IHC is not clear. Because the historical and clinical trial data on which treatment decisions are based have relied on H&E staining, the Panel believes that current treatment decisions should be made based solely on H&E staining (category 3). In the uncommon situation in which H&E staining is equivocal, reliance on the results of cytokeratin IHC is reasonable.

Level I or II axillary dissection is an appropriate staging study in women with invasive breast cancer. Although the option of sentinel lymph node mapping and excision is preferred by the Panel over axillary lymph node dissection as the initial axillary lymph node staging for women with clinically node-negative stage I or stage II breast cancer, it is not a mandatory replacement for a level I and II axillary dissection. Axillary lymph node dissection remains indicated in women found to have axillary lymph node involvement on sentinel lymph node excision. Traditional level I and level II axillary dissection required that at least 10 lymph nodes should be provided for pathologic evaluation to accurately stage the axilla.\cite{89,90} Axillary dissection should be extended to include level III nodes only if gross disease is apparent in the level I or II nodes.

Furthermore, in the absence of definitive data demonstrating superior survival with axillary lymph node dissection or sentinel lymph node resection, these procedures may be considered optional in patients who have particularly favorable tumors, patients for whom the selection of adjuvant systemic therapy is unlikely to be affected by the results of the procedure, elderly patients, and patients with serious co-morbid conditions (see BINV-D). Women who do not undergo axillary dissection or axillary lymph node irradiation are at increased risk for ipsilateral lymph node recurrence.\cite{91} Women who undergo mastectomy are appropriate candidates for breast reconstruction.

**Preoperative chemotherapy for large clinical stage IIA and IIB tumors and T3N1M0 tumors**

Preoperative chemotherapy should be considered for women with large clinical stage IIA, stage IIB, and T3N1M0 tumors who meet the criteria for breast-conserving therapy except for tumor size and who wish to undergo breast-conserving therapy. In the available clinical trials of preoperative chemotherapy, pretreatment biopsies have been limited to core needle biopsy or FNA cytology. Therefore, in patients anticipated to receive preoperative chemotherapy, core or FNA biopsy of the breast...
tumor should be performed, and core or FNA biopsy of clinically suspicious axillary lymph nodes should be considered. Preoperative chemotherapy is not indicated unless invasive breast cancer is confirmed. The current guideline lists pre-chemotherapy sentinel lymph node resection as the preferred option for surgical axillary staging in those women with clinically negative ipsilateral axillary examinations (see BINV-C). If the sentinel lymph node is histologically negative, omission of the axillary dissection may be considered at the time of local, surgical therapy. If the sentinel lymph node is histologically positive, then level I and II axillary dissection should be performed at the time of definitive surgical therapy. If a pre-chemotherapy sentinel lymph node excision is not performed, then a level I and II axillary dissection (category 2A) or sentinel lymph node excision (category 3) (with level I and II axillary dissection if sentinel lymph node is positive) should be performed at the time of definitive surgical therapy.

In some patients, preoperative chemotherapy results in sufficient tumor response that breast-conserving therapy becomes possible. Because complete or near-complete clinical responses are common, the use of percutaneously placed clips into the breast under mammographic or ultrasound guidance or other method of localizing pre-chemotherapy tumor volume aids in the post-chemotherapy resection of the original area of tumor and is encouraged. The results of the NSABP B-18 trial show that breast conservation rates are higher after preoperative chemotherapy. However, preoperative chemotherapy has no demonstrated disease specific survival advantage over postoperative adjuvant chemotherapy in patients with stage II tumors. NSABP B-27 is a 3-arm, randomized phase III trial of women with invasive breast cancer treated with preoperative doxorubicin and cyclophosphamide (AC) chemotherapy for 4 cycles followed by local therapy alone, preoperative AC followed by preoperative docetaxel for 4 cycles followed by local therapy, or AC followed by local therapy followed by 4 cycles of postoperative docetaxel. Results from this study which involved 2411 women documented a higher rate of complete pathologic response at the time of local therapy in patients treated preoperatively with 4 cycles of AC followed by 4 cycles of docetaxel versus 4 cycles of preoperative AC. Disease-free survival and overall survival have not been shown to be superior following docetaxel treatment in B-27. A disease-free survival advantage was observed (hazard ratio 0.71; 95% CI, 0.55 – 0.91; P=0.007) favoring preoperative versus postoperative docetaxel in the subset of patients experiencing a clinical partial response to AC.

A number of chemotherapy regimens have been studied as preoperative chemotherapy in the neoadjuvant setting. The Panel believes that the regimens recommended in the adjuvant setting (see BINV-H) are appropriate to consider in the preoperative chemotherapy setting. In women with HER2-positive tumors treated with neoadjuvant chemotherapy, the addition of neoadjuvant trastuzumab to paclitaxel followed by FEC chemotherapy was associated with an increase in the pathologic complete response rate from 26% to 65.2% (P=0.016). Thus, the incorporation of trastuzumab into neoadjuvant chemotherapy regimens appears important in HER2-positive tumors.

Several randomized trials have assessed the value of neoadjuvant endocrine therapy in postmenopausal women with estrogen receptor-positive breast cancer. These studies have generally compared the rates of objective response and rates of breast-conserving surgery among treatment with tamoxifen, anastrozole, anastrozole plus tamoxifen, or letrozole. These studies consistently demonstrate that the use of either anastrozole or letrozole alone provides superior rates of breast-conserving surgery and usually objective response. On the basis of these trials, preoperative hormonal therapy with an aromatase inhibitor is an option in the treatment of postmenopausal women with hormone receptor-positive disease.
If the tumor responds to preoperative chemotherapy, lumpectomy plus (if pre-chemotherapy sentinel lymph node staging was not done or was positive) axillary lymph node dissection (category 2A) or (if pre-chemotherapy axillary lymph node staging not performed) sentinel lymph node procedure (category 3) may be considered if the requirements for breast-conserving therapy are fulfilled (see BINV-11; BINV-12). If a pre-chemotherapy sentinel lymph node procedure was performed and the sentinel lymph node was pathologically negative, then further axillary lymph node staging is not necessary. If a pre-chemotherapy sentinel lymph node procedure was performed and the sentinel lymph node was positive, then a level I/II axillary lymph node dissection should be performed. Breast-conserving surgery should be followed by individualized chemotherapy such as taxanes (category 2B) as well as breast and regional lymph node irradiation. Whether the internal mammary lymph nodes should be included in the regional lymph node field generated substantial controversy among Panel members (category 3). If after several cycles of preoperative chemotherapy, the tumor fails to respond, the response is minimal, or if the disease progresses at any point, a mastectomy plus axillary dissection, with or without breast reconstruction, should be performed. Postoperative treatment for these patients consists of individualized chemotherapy, endocrine therapy in women with estrogen and/or progesterone receptor-positive tumors, and RT to the chest wall and supraclavicular lymph nodes. Inclusion of the internal mammary lymph nodes in the radiotherapy field can be considered, but this recommendation generated substantial controversy among Panel members (category 3). Postmastectomy RT in patients with T2N0M0 tumors may be considered optional.

**Radiation therapy after mastectomy**

**Node positive disease**

Three randomized clinical trials have shown that a disease-free and overall survival advantage is conferred by the addition of chest wall and regional lymph node irradiation in women with positive axillary lymph nodes after mastectomy and axillary lymph node dissection. In these trials, not only the ipsilateral chest wall but also the ipsilateral local-regional lymph nodes were irradiated. These studies contrast, however, with a number of other studies, including a randomized trial from an NCCN institution that failed to show a survival advantage with postmastectomy chest wall and regional node irradiation. However, on the basis of the 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 women with such cancers.

For women with 1 to 3 involved axillary lymph nodes, the Guidelines recommend consideration of radiation to the chest wall and supraclavicular area after chemotherapy (category 1), with consideration also given to the inclusion of the ipsilateral internal mammary field (category 3). The recommendation for chest wall and supraclavicular irradiation in women with 1-3 involved axillary lymph nodes generated substantial controversy among Panel members. Some Panel members believe chest wall and supraclavicular irradiation should be used routinely after mastectomy and chemotherapy in this subgroup of patients. However, other Panel members believe radiation should be considered in this setting but should not be mandatory given the studies that do not show an advantage. This is an unusual situation in which high-level evidence (category 1) exists but is contradictory. Women with 1 to 3 involved axillary lymph nodes and with tumors greater than 5 cm or with tumors with positive pathologic margins postmastectomy should receive post-chemotherapy RT to the chest wall and supraclavicular areas (category 1) with consideration of inclusion of the ipsilateral internal mammary field (category 3).
There is considerable disagreement regarding the inclusion of the ipsilateral internal mammary field. Some Panel members believe that irradiation of the internal mammary nodes is unnecessary and produces too much morbidity. Others believe internal mammary field irradiation should be included, as it was in the studies that demonstrated an advantage for postmastectomy, post-chemotherapy RT. Therefore, this recommendation is identified as category 3.

Women with 4 or more positive axillary lymph nodes are at substantially increased risk for local recurrence of disease. The use of postmastectomy, post-chemotherapy chest wall and regional lymph node irradiation is recommended (category 1). The use of prophylactic chest wall RT in this setting substantially reduces the risk of local recurrence.\(^6\) Again, there was substantial disagreement among Panel members regarding the inclusion of the ipsilateral internal mammary field (category 3).

**Node negative disease**
Features in node-negative tumors that predict a high rate of local recurrence include primary tumors greater than 5 cm and close (less than 1 mm) or positive pathologic margins. Chest wall RT is recommended in patients with negative axillary lymph nodes and tumors greater than 5 cm or with positive pathologic margins.\(^{103}\) Consideration should be given to radiation to the ipsilateral supraclavicular area (category 2B) and to the ipsilateral internal mammary lymph nodes (category 3). Chest wall RT should be considered for patients with negative axillary lymph nodes and close (less than 1 mm) pathologic margins. RT is not recommended for patients with negative margins, tumors 5 cm or smaller, and no positive axillary lymph nodes.

**Systemic adjuvant therapy**
After surgical treatment, adjuvant systemic therapy should be considered. The most recently published updates of the Early Breast Cancer Trialists’ Collaborative Group overview analyses of adjuvant polychemotherapy and tamoxifen show convincing reductions in the odds of recurrence and of death in all age groups under 70 years for polychemotherapy and in all age groups for tamoxifen.\(^2\) Thus, for those under age 70, the current Guidelines recommend adjuvant therapy without regard to patient age (category 1). The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of the therapy and comorbidity.\(^{104, 105}\) The decision-making process requires a collaboration involving the health care team and the patient.

**Estimating risk of relapse or death and benefits of systemic treatment**
A number of prognostic factors predict for future recurrence or death from breast cancer. The strongest prognostic factors are patient age, comorbidity, tumor size, tumor grade, number of involved axillary lymph nodes, and possibly HER2 tumor status. Algorithms have been published estimating rates of recurrence,\(^{104}\) and a validated computer-based model (Adjuvant! Online; [www.adjuvantonline.com](http://www.adjuvantonline.com)) is available to estimate 10-year disease-free and overall survival that incorporates all of the above prognostic factors except for HER2 tumor status.\(^{105, 106}\) These tools aid the clinician in objectively estimating outcome with local treatment only, and also assist in estimating the absolute benefits expected from systemic adjuvant endocrine therapy and chemotherapy. These estimates may be utilized by the clinician and patient in their shared decision-making regarding the toxicities, costs, and benefits of systemic adjuvant therapy.\(^{107}\)

Use of DNA microarray technologies to characterize breast cancer has allowed the development of classification systems of breast cancer by
gene expression profile. Five major subtypes of breast cancer have been identified by DNA microarray gene expression profiling: ER-positive/HER2-negative (Luminal A and Luminal B subtypes); ER-negative/HER2-negative (Basal subtype); HER2-positive; and tumors that have characteristics similar to normal breast tissue (Normal breast-like). In retrospective analyses, these gene expression subtypes are associated with differing relapse-free and overall survival. A similar approach has been used to define more limited sets of genes for prognostic and predictive purposes.

Another gene-based approach is the multi-gene assay using reverse transcription polymerase chain reaction (RT-PCR) on RNA isolated from paraffin-embedded breast cancer tissue (Oncotype Dx). On retrospective analysis of two trials (NSABP B-14 and B-20) performed in women with hormone receptor-positive, axillary lymph node-negative invasive breast cancer, this assay system was able to quantify risk of recurrence as a continuous variable (eg, Oncotype Dx recurrence score) and to predict responsiveness to both tamoxifen and CMF or methotrexate/5-fluorouracil/leucovorin chemotherapy.

A comparison of simultaneous analyses of breast cancer tumors using 5 different gene-expression models indicated that 4 of these methods provided similar predictions of clinical outcome.

While many of the DNA microarray technologies are able to stratify patients into prognostic and/or predictive subsets on retrospective analysis, the gene subsets appear to differ from study to study, and prospective clinical trials testing the utility of these techniques have yet to be reported. The Panel anticipates that the use of gene microarrays or RT-PCR analysis of RNA will play an important role in providing information regarding prognostic and predictive characteristics of subsets of patients with breast cancer. The Panel awaits additional studies prior to issuing a specific recommendation regarding this or similar assays.

**Axillary lymph node negative tumors**

Small tumors (up to 0.5 cm in greatest diameter) that do not involve the lymph nodes are so favorable that adjuvant systemic therapy is of minimal incremental benefit and is not recommended as treatment of the invasive breast cancer. Tamoxifen may be considered to reduce the risk of a second contralateral breast cancer, especially in those with estrogen receptor-positive disease. The NSABP database demonstrated a correlation between the estrogen receptor status of a new contralateral breast tumor and the original primary tumor, which reinforced the notion that tamoxifen is unlikely to be an effective strategy to reduce the risk of contralateral breast cancer in patients diagnosed with estrogen receptor-negative tumors. Patients with invasive ductal or lobular tumors 0.6 to 1 cm in diameter and no lymph node involvement may be divided into patients with a low risk of recurrence and those with unfavorable prognostic features that warrant consideration of adjuvant therapy. Unfavorable prognostic features include intramammary angiolymphatic invasion, high nuclear grade, high histological grade, HER2-positive status, or hormone receptor-negative status (category 2B). The use of endocrine therapy and chemotherapy in these relatively lower risk subsets of women must be based on balancing the expected absolute risk reduction and the individual patient’s willingness to experience toxicity to achieve that incremental risk reduction.

Patients with lymph node involvement or with tumors 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 breast cancer tumors greater than 1 cm, endocrine therapy with chemotherapy is recommended (category 1). The incremental benefit of combination chemotherapy in patients with lymph node-negative, hormone receptor-positive breast cancer may be
relatively small. Therefore, the Panel recommends that tumor hormone receptor status be included as one of the factors considered when making chemotherapy-related treatment decisions for patients with node-negative, hormone receptor-positive breast cancer. Patients for whom this evaluation may be especially important are those with tumors characterized as 0.6-1.0 cm and hormone receptor-positive with unfavorable features, or greater than 1 cm and hormone receptor-positive and HER2-negative (see BINV-5; BINV-6). However, chemotherapy should not be withheld from these patients solely on the basis of estrogen receptor-positive tumor status.2,119,120

The use of both endocrine therapy and chemotherapy must be based on balancing the expected absolute risk reduction and the individual patient’s willingness to experience toxicity to achieve that incremental risk reduction. The use of genomic/gene expression array data which also incorporate additional prognostic/predictive biomarkers (eg, Oncotype Dx recurrence score) may provide additional prognostic and predictive information beyond anatomic staging and determination of ER/PR and HER2 status. Assessment of the role of the genomic/gene expression array technology is difficult because of the retrospective nature of the studies, the evolution of chemotherapy and hormone therapy regimens, and the overall more favorable prognosis of the patients with lymph node-negative disease compared with those enrolled in the historically-controlled clinical trials. Some NCCN institutions consider performing RT-PCR analysis (eg, Oncotype DX assay) to further refine risk stratification for adjuvant chemotherapy for patients with node-negative, estrogen receptor-positive, HER2-negative breast cancers greater than 0.5 cm, whereas others do not (category 2B). The Panel overall continues to await the results of additional studies before a definitive recommendation may be made in the guideline on the role of the various genomic/gene expression array techniques in risk stratification and in the treatment decision making process.

**Axillary lymph node positive tumors**

Patients with lymph node-positive disease are candidates for chemotherapy and, if the tumor is hormone receptor-positive, for the addition of endocrine therapy (category 1). In postmenopausal women, with hormone receptor-positive disease, an aromatase inhibitor should be utilized either as initial adjuvant therapy, sequential with tamoxifen, or as extended therapy following tamoxifen. In premenopausal women, adjuvant tamoxifen is preferred. If both chemotherapy and tamoxifen are used, data from the Intergroup trial 0100 suggest that delaying initiation of tamoxifen until after completion of chemotherapy improves disease-free survival compared with concomitant administration.120 Consequently, chemotherapy followed by endocrine therapy should be the preferred therapy sequence.

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

**Guideline stratification for systemic therapy**

The current version of the Guidelines first recognizes subsets of patients with early breast cancer of the usual histologies based upon responsiveness to endocrine therapy and trastuzumab (ie, hormone receptor status, HER2 status) (see BINV-4). Patients are then further stratified based upon risk for recurrence of disease based upon anatomic and pathologic characteristics (ie, tumor grade, tumor size, axillary lymph node status, angiolymphatic invasion) (see BINV-5; BINV-6; BINV-7; BINV-8).

**Adjuvant endocrine therapy**

The NCCN Guidelines call for the determination of estrogen and progesterone receptor content in all primary invasive breast cancers. Patients with invasive breast cancers that are estrogen or progesterone receptor positive should be considered for adjuvant endocrine therapy.
regardless of patient age, lymph node status, or whether or not adjuvant chemotherapy is to be administered. Selected studies suggest that HER2-positive breast cancers may be less sensitive to some hormonal therapies, although other studies have failed to confirm this finding. Given the inconsistency of these data and the favorable toxicity profile of the available endocrine therapies, the Panel recommends the use of adjuvant endocrine therapy in the majority of women with hormone receptor-positive breast cancer regardless of menopausal status, age, or HER2 status of the tumor. The exceptions to this recommendation are patients with lymph node-negative cancers less than or equal to 0.5 cm or 0.6 to 1.0 cm in diameter with favorable prognostic features where the prognosis is so favorable that the benefits of adjuvant endocrine therapy are very small.

The most firmly established adjuvant endocrine therapy is tamoxifen for both premenopausal and postmenopausal women. In women with estrogen receptor-positive breast cancer, adjuvant tamoxifen decreases the annual odds of recurrence by 39% and the annual odds of death by 31% irrespective of the use of chemotherapy, patient age, menopausal status, or axillary lymph node status. Prospective, randomized trials demonstrate that the optimal duration of tamoxifen appears to be five years. In patients receiving both tamoxifen and chemotherapy, chemotherapy should be given first, followed by sequential tamoxifen.

Several studies have evaluated aromatase inhibitors in the treatment of postmenopausal women with early-stage breast cancer. These studies have utilized the aromatase inhibitors as initial adjuvant therapy, as sequential therapy following 2-3 years of tamoxifen, or as extended therapy following 4.5 - 6 years of tamoxifen. The aromatase inhibitors are not active in the treatment of women with functioning ovaries and should not be used in women whose ovarian function cannot be reliably assessed owing to treatment-induced amenorrhea (see Definition of Menopause). The results from two prospective, randomized clinical trials have provided early evidence of an overall survival benefit for patients with early-stage breast cancer receiving initial endocrine therapy with tamoxifen followed sequentially by anastrozole or exemestane when compared with tamoxifen as the only endocrine therapy. In addition, the National Cancer Institute Canada Clinical Trials Group (NCIC CTG) MA-17 trial demonstrated a survival advantage with extended therapy with letrozole compared with placebo in women with axillary lymph node-positive (but not lymph node-negative), estrogen receptor-positive breast cancer. Tamoxifen and aromatase inhibitors have different side effect profiles. Both contribute to hot flashes, night sweats and may cause vaginal dryness. Aromatase inhibitors are more commonly associated with musculoskeletal symptoms, osteoporosis, and increased rate of bone fracture, while tamoxifen is associated with an increased risk of uterine cancer and deep venous thrombosis.

Two studies have examined initial adjuvant endocrine treatment with either tamoxifen or an aromatase inhibitor. The Arimidex, Tamoxifen, Alone or in Combination Trial (ATAC Trial) demonstrated that anastrozole is superior to tamoxifen or the combination of tamoxifen and anastrozole in the adjuvant endocrine therapy of postmenopausal women with hormone receptor-positive breast cancer. With a median of 68 months follow-up, results in 9366 postmenopausal women with early breast cancer enrolled in the ATAC Trial demonstrated fewer recurrences (hazard ratio 0.87; 95% CI 0.78 - 0.97; P = 0.01) with anastrozole compared with tamoxifen. In the subset of women with hormone receptor-positive breast cancer the benefit was greater (hazard ratio 0.83; 95% CI 0.73 - 0.94; P = 0.005). No difference in survival has been observed (hazard ratio 0.97; 95% CI, 0.85-1.12; P=0.7). A retrospective evaluation of the ATAC Trial data suggests that women with estrogen receptor-positive, progesterone receptor-negative breast cancer may experience a greater benefit.
favoring anastrozole than other hormone receptor combinations.\textsuperscript{135} Patients in the combined tamoxifen and anastrozole group gained no benefit over those in the tamoxifen group, suggesting a possible deleterious effect from the weak estrogenic effect of tamoxifen in patients with near complete elimination of endogenous estrogen levels. ATAC Trial sub-protocols show a lesser effect of anastrozole compared with tamoxifen on endometrial tissue,\textsuperscript{136} similar effects of anastrozole and tamoxifen on quality of life, with most patients reporting that their overall quality of life was not significantly impaired,\textsuperscript{137} a greater loss of bone mineral density with anastrozole,\textsuperscript{138} a small pharmacokinetic interference of anastrozole in the presence of tamoxifen of unclear significance,\textsuperscript{139} and no evidence for an interaction between prior chemotherapy and anastrozole.\textsuperscript{140}

Breast International Group (BIG) 1-98 is a randomized trial testing the use of tamoxifen alone for 5 years, letrozole alone for 5 years, or tamoxifen for 2 years followed sequentially by letrozole for 3 years, or letrozole for 2 years followed sequentially by tamoxifen for 3 years. An early analysis compared tamoxifen alone versus letrozole alone, including those patients in the sequential arms during their first two years of treatment only.\textsuperscript{141} With 8,010 women included in the analysis, disease-free survival was superior in the letrozole treated women (hazard rate 0.81; 95% CI 0.70 – 0.93; log rank \(P=0.003\)). No interaction between progesterone receptor expression and benefit was observed. No difference in overall survival has been observed.

Four trials have studied the use of tamoxifen for 2-3 years followed sequentially by a third generation aromatase inhibitor versus continued tamoxifen. The Italian Tamoxifen Anastrozole (ITA) Trial randomized 426 postmenopausal women with breast cancer who had completed 2-3 years of tamoxifen to either continue tamoxifen or to switch to anastrozole to complete a total of 5 years of endocrine therapy.\textsuperscript{142} The hazard rate for relapse strongly favored sequential treatment with anastrozole (hazard ratio 0.35; 95% CI, 0.18 - 0.68; \(P=0.001\)) with a trend towards fewer deaths (\(P=0.10\)).\textsuperscript{142} The Intergroup Exemestane Study (IES) trial randomized 4742 postmenopausal women with breast cancer who had completed a total of 2-3 years of tamoxifen to either continue tamoxifen or to switch to exemestane to complete a total of 5 years of endocrine therapy.\textsuperscript{143} The results at a median of 30.6 months of follow-up demonstrated the superiority of sequential exemestane in disease-free survival (hazard ratio 0.68; 95% CI 0.56 - 0.82; log rank \(P<0.001\)) with no difference in overall survival (hazard ratio 0.88; 95% CI 0.67 - 1.16; log rank \(P=0.37\)). Similar to the ATAC Trial, women with estrogen receptor-positive, progesterone receptor-negative breast cancer appeared to benefit to a greater degree in disease-free survival in comparison to other receptor subsets (hazard ratio in ER-positive, PR-negative 0.58; 95% CI 0.38 - 0.90; \(P\) not stated). However, results from the IES trial after 58 months of follow-up indicated that switching to exemestane was associated with statistically significant beneficial effects on both disease-free survival (hazard ratio 0.74; 95% CI 0.64-0.85; \(P<0.0001\)) and overall survival (hazard ratio 0.83).\textsuperscript{130} A prospectively planned, combined analysis of 3,224 patients enrolled in the Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial 8 and the Arimidex Nolvadex® (ARNO 95) trial has also been reported.\textsuperscript{144} Patients in this combined analysis had been randomized following 2 years of tamoxifen to complete 5 years of adjuvant tamoxifen or to 3 years of anastrozole. With 28 months median follow-up available, event-free survival was superior with cross-over to anastrozole (hazard ratio 0.60; 95% CI 0.44-0.81; \(P=0.0009\)). No statistically significant difference in survival has been observed. An analysis of the ARNO 95 trial alone after 30.1 months of follow-up demonstrated that switching from tamoxifen to anastrozole was associated with significant increases in both disease-free survival (hazard ratio 0.61; 95% CI 0.40-0.93; \(P=0.023\)) and overall survival (hazard ratio 0.48; 95% CI 0.25-0.91; \(P=0.025\)).\textsuperscript{131}
Results of the MA-17 trial in 5187 women who had completed 4.5-6 years of adjuvant tamoxifen demonstrated that extended therapy with letrozole provides benefit in postmenopausal women with hormone receptor-positive, early breast cancer.\textsuperscript{132,145} At a median follow-up of 2.5 years, the results showed fewer recurrences or new contralateral breast cancers with extended letrozole (hazard ratio 0.58; 95% CI 0.45 - 0.76; \( P<0.001 \)). No difference in overall survival was demonstrated (hazard rate 0.82; 95% CI 0.57-1.19; \( P=0.3 \)), although there was a survival advantage in the subset of patients with axillary lymph node-positive disease (hazard rate 0.61; 95% CI 0.38-0.98; \( P=0.04 \)). A formal quality of life analysis demonstrated reasonable preservation of quality of life during extended endocrine therapy, although women may experience ongoing menopausal symptoms and loss of bone mineral density.\textsuperscript{146,147}

The differences in design and patient populations among the studies of the aromatase inhibitors do not allow for the direct comparison of the results of these studies. Thus, it is not known whether initial, sequential, or extended use of adjuvant aromatase inhibitors is the optimal strategy. The optimal duration of aromatase inhibitor treatment is also not known, nor is the optimal use vis-à-vis chemotherapy established. Further, the long-term (greater than 5 year) safety and efficacy of these agents are still under investigation. The various studies are consistent in demonstrating that the use of a third generation aromatase inhibitor in postmenopausal women with hormone receptor-positive breast cancer lowers the risk of recurrence, including ipsilateral breast tumor recurrence, contralateral breast cancer, and distant metastatic disease, compared to tamoxifen alone when the aromatase inhibitor is used as initial adjuvant therapy, sequential therapy, or extended therapy. Thus, the current version of the guideline recommends that postmenopausal women with early breast cancer receive an aromatase inhibitor as initial adjuvant therapy, sequential with tamoxifen, or as extended therapy in those situations where endocrine therapy is to be utilized. The guideline recommends the use of the specific aromatase inhibitor(s) that have been demonstrated to be superior to tamoxifen alone in the specific clinical setting, although the Panel finds no compelling evidence that there are meaningful efficacy or toxicity differences between anastrozole, letrozole, and exemestane. In postmenopausal women, the use of tamoxifen alone for 5 years is limited to those who decline or who have a contraindication to aromatase inhibitors (see BINV-G).

It should be re-emphasized that the aromatase inhibitors are not active in women with functioning ovaries, and premenopausal women should not be given therapy with an aromatase inhibitor outside the confines of a clinical trial. Women who are premenopausal at the time of diagnosis and who become amenorrheic with chemotherapy may have continued estrogen production from the ovaries in the absence of menses. Serial assessment of circulating LH, FSH, and estradiol to assure a true postmenopausal status is mandatory if this subset of women are to be considered for therapy with an aromatase inhibitor\textsuperscript{148,149} (see BINV-I).

**Adjuvant cytotoxic chemotherapy**

A number of combination chemotherapy regimens are appropriate to consider when adjuvant cytotoxic chemotherapy is utilized. These regimens include fluorouracil, doxorubicin, and cyclophosphamide (FAC/CAF) or cyclophosphamide, epirubicin, and fluorouracil (CEF); doxorubicin or epirubicin and cyclophosphamide (AC/EC); docetaxel, doxorubicin, and cyclophosphamide (TAC); doxorubicin or epirubicin followed by CMF; cyclophosphamide, methotrexate and fluorouracil (CMF); AC with sequential paclitaxel or docetaxel administered by a variety of schedules; doxorubicin, paclitaxel, cyclophosphamide each as a single agent for four cycles given every 2 weeks with filgrastim support (Dose-dense A – T– C); FEC followed by docetaxel; and docetaxel plus cyclophosphamide (TC). The current version of the guideline does not distinguish appropriate chemotherapy regimens by axillary lymph node status. Recent studies document substantial improvement in outcome with the incorporation of trastuzumab in the...
adjuvant treatment of HER2-positive breast cancer (see Adjuvant trastuzumab therapy). The guideline includes specific representative doses and schedules for the recommended adjuvant chemotherapy regimens (see BiNV-H).

Studies of CMF chemotherapy versus no chemotherapy have shown disease-free and overall survival advantages with CMF chemotherapy.156 Studies using CAF/FAC (cyclophosphamide, doxorubicin, 5-fluorouracil) chemotherapy have shown that the use of full-dose chemotherapy regimens is important.151 In the Early Breast Cancer Trialists’ overview of polychemotherapy, comparison of anthracycline-containing regimens with CMF showed a 12% further reduction in the annual odds of recurrence (P = 0.006) and an 11% further reduction in the annual odds of death (P = 0.02) with anthracycline-containing regimens.150 Based on these data, the Panel qualified the appropriate chemotherapy regimens by the statement that anthracycline-containing regimens are preferred for node-positive patients. The Early Breast Cancer Trialists’ analysis, however, did not consider the potential interaction between HER2 tumor status and efficacy of anthracycline-containing versus CMF chemotherapy regimens. Retrospective analysis has suggested that the superiority of anthracycline-containing chemotherapy may be limited to the treatment of those breast cancers that are HER2-positive.50,52,125,152,153 The retrospective finding across several clinical trials that anthracycline-based chemotherapy may be more efficacious in patients whose tumors are HER2-positive,49,50,52,53,76 has led to a footnote stating that anthracycline-based chemotherapy may be superior to non-anthracycline-containing regimens in the adjuvant treatment of such patients (see BiNV-H).

Doxorubicin and cyclophosphamide chemotherapy for 4 cycles has been studied in randomized trials, resulting in relapse-free and overall survival equivalent to CMF chemotherapy.154-156 No benefit from dose escalation of either doxorubicin or cyclophosphamide was shown.157,158 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.159,160

The results of two randomized trials comparing AC chemotherapy with or without sequential paclitaxel chemotherapy in women with axillary node-positive breast cancer suggest improved disease-free rates and results from one of the trials showed an improvement in overall survival with the addition of paclitaxel.158,161 On retrospective analysis, the apparent advantage of the paclitaxel-containing regimen appears greater in women with estrogen receptor-negative breast cancers.

A randomized trial evaluated the use of concurrent versus sequential chemotherapy (doxorubicin followed by paclitaxel followed by cyclophosphamide versus doxorubicin plus cyclophosphamide followed by paclitaxel) given either every two weeks with filgrastim support versus every three weeks. The results show no significant difference between the two chemotherapy regimens, but demonstrate a 26% reduction in hazard of recurrence (P=0.01) and a 31% reduction in the hazard of death (P=0.013) for the dose-dense regimens.162

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 receive classic CMF therapy versus CEF chemotherapy using high-dose epirubicin. Both ten-year relapse-free survival (52% vs. 45%; P = 0.007) and overall survival (62% vs. 58%; P =0.085) favored the CEF arm of the trial.163 The second trial compared CEF given all intravenously every 3 weeks at 2 dose levels of epirubicin (50 mg/m² vs. 100 mg/m²) 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 mg/m² arm.164 A recent trial compared 2
Recent retrospective studies have evaluated the potential interaction of chemotherapy benefit and estrogen receptor status.\textsuperscript{2,119} These studies assessed the effect of chemotherapy on the risk of breast cancer recurrence in patients with estrogen receptor-positive tumors receiving adjuvant endocrine therapy when compared with patients with estrogen receptor-negative tumor status not undergoing adjuvant endocrine therapy. These analyses suggest that the benefits of chemotherapy are significantly greater in patients with estrogen receptor-negative disease. For example, the results of Berry et al. demonstrated that 22.8% more patients with estrogen receptor-negative tumors survived without disease for 5 years if they received chemotherapy; this benefit was only 7% for patients with estrogen receptor-positive tumors receiving chemotherapy.\textsuperscript{119} The guideline has therefore been modified to include a recommendation for endocrine therapy and consideration of chemotherapy for patients with node-negative disease and tumors characterized as estrogen receptor-positive which are greater than 1 cm and HER2-negative (see BINV-6). Previous versions of the guideline recommended the use of endocrine therapy plus chemotherapy in all such patients.

### Adjuvant trastuzumab therapy

Trastuzumab is a humanized, monoclonal antibody with specificity for the extracellular domain of the human epidermal growth factor receptor 2 (HER2/neu; HER2).\textsuperscript{170} Results of five randomized trials testing trastuzumab as adjuvant therapy were recently reported.\textsuperscript{55-58} In NSABP B-31 patients with HER2-positive, node-positive breast cancer were randomly assigned to 4 cycles of AC every three weeks followed by paclitaxel 4 cycles every three weeks or the same regimen with 52 weeks of trastuzumab commencing with the paclitaxel. In the North Central Cancer Treatment Group (NCCTG) N9831 trial, HER2-positive breast cancer that was node-positive, or, if node-negative, with primary tumors greater than 1 cm in size if ER and PR negative or greater than 2 cm in size if ER- or PR-positive, were similarly randomized except...
that paclitaxel was given by a low dose weekly schedule for 12 weeks and a third arm delayed trastuzumab until the completion of paclitaxel. The B-31 and NCCTG N9831 trials were jointly analyzed with the merged control arms for both trials compared with the merged arms using trastuzumab begun concurrently with the paclitaxel. There were 3,351 patients included in the joint analysis performed at 2 years median follow-up. A 52% reduction in the risk of recurrence (hazard ratio 0.48; 95% CI 0.39-0.59; log-rank P < 0.001) and a 33% reduction in the risk of death (hazard ratio 0.67; 95% CI 0.48-0.93; log-rank P = 0.015) were documented. Similar significant effects on disease-free survival were observed when results of the NSABP B-31 and NCCTG N9831 trials were analyzed separately. Cardiac toxicity was increased in patients treated with trastuzumab.

A third trial (HERA) (N=5081) tested trastuzumab for one or for two years compared to none following all local therapy and a variety of standard chemotherapy regimens. At a median follow-up of one year, comparing one year versus not of trastuzumab, trastuzumab resulted in a 46% reduction in the risk of recurrence compared to no trastuzumab (hazard ratio 0.54; 95% CI 0.43-0.67; P < 0.0001), no difference in overall survival, and acceptable cardiac toxicity. The two year data are not yet reported.

All of the adjuvant trials of trastuzumab demonstrate clinically significant improvements in disease-free survival, and the combined analysis from the NSABP B31 and NCCTG N9831 trials, demonstrated significant improvement in overall survival with the use of trastuzumab in patients with high-risk, HER2-positive breast cancer. Therefore, regimens from each of these trials are included as trastuzumab-containing adjuvant regimen choices in the guideline (category 1) (see BINV-H). The Panel recommends AC followed by paclitaxel with trastuzumab for 1 year commencing with the first dose of paclitaxel as the preferred trastuzumab-containing adjuvant regimen since the efficacy of this regimen has been demonstrated in two randomized clinical trials, and it has been associated with significant improvements in overall survival. Since patients with borderline FISH (Pathvysion®) scores of greater than 2.0 to 2.2 HER2 genes/chromosome 17/cell in early-stage breast cancer were eligible for the adjuvant trials, the Panel
cannot recommend exclusion of these patients from adjuvant treatment with trastuzumab if HER2 tumor status remains equivocal following retesting by the same or a complementary method (see BINV-A).

In the adjuvant trastuzumab trials, the rates of grade III/IV congestive heart failure (CHF) or cardiac-related death for patients receiving treatment regimens containing trastuzumab ranged from 0% (FinHer trial) to 4.1% (NSABP B-31 trial) overall. The frequency of cardiac dysfunction appears to be related to both age and baseline left ventricular ejection fraction. The acceptable rate of significant cardiac toxicity observed in the trastuzumab adjuvant trials in part reflects rigorous monitoring for cardiac dysfunction.

**Adjuvant therapy of favorable histology tumors**
The Guidelines provide systemic treatment recommendations for the favorable-histology invasive breast cancers, such as tubular and colloid cancers, based on tumor size and axillary lymph node status (see BINV-9). If used, the treatment options for endocrine therapy, chemotherapy, and sequencing of treatment with other modalities are similar to those of the usual histology breast cancers. The vast majority of tubular breast cancers are both estrogen receptor-positive and HER2-negative. Thus, the pathology evaluation and accuracy of the estrogen receptor and/or HER2 determination should be questioned if a tubular breast cancer is found to be estrogen receptor-negative and/or HER2-positive. The Panel acknowledges that prospective data regarding systemic adjuvant therapy of favorable histology tumors is lacking. Medullary carcinoma is an uncommon variant of infiltrating ductal carcinoma characterized by high nuclear grade, lymphocytic infiltration, a pushing tumor border, and the presence of a syncytial growth pattern. It was previously thought that medullary carcinoma has a lower potential for metastases and a better prognosis than typical infiltrating ductal carcinoma. However, the best available evidence suggests that the risk of metastases equals that of other high-grade carcinomas, even for cases that meet all the pathologic criteria for typical medullary carcinoma. Furthermore, typical medullary carcinoma is uncommon, and there is marked interobserver variation in diagnosing this entity. Many cases classified as medullary carcinoma do not have all the pathologic features on subsequent pathologic review. Given these facts, there is concern that patients may be harmed if a high-grade infiltrating ductal carcinoma is misclassified as typical medullary carcinoma and this classification used as the basis for withholding otherwise indicated adjuvant systemic therapy. Therefore, the NCCN Panel believes that including medullary carcinoma with other special histology cancers that carry a very favorable prognosis and often do not require systemic therapy is not appropriate. The Panel recommends that cases classified as medullary carcinoma be treated as other infiltrating ductal carcinomas based on tumor size, grade, and lymph node status.

**Stage III Invasive Breast Cancer**
The staging evaluation for patients with stage III invasive breast cancer is similar to the one for patients with stage I or stage II disease. The workup includes history and physical exam, a complete blood cell count, platelet count, a bone scan (category 2B), chest imaging, pathology review, pre-chemotherapy determination of tumor ER/PR receptor status and HER2 status, diagnostic bilateral mammogram and breast ultrasound as clinically warranted, and an abdominal CT, ultrasound, or MRI scan (category 2B), even in the absence of symptoms, liver enzyme abnormalities, or abnormal alkaline phosphatase.

**Operable locally advanced breast cancer (clinical stage T3N1M0)**
Locally advanced breast cancer describes a subset of invasive breast cancer where the initial clinical and radiographic evaluation documents advanced disease confined to the breast and regional lymph nodes. The AJCC clinical staging system used in these Guidelines and for the
determination of operability is recommended and locally advanced disease is represented by the stage III category. Patients with stage III disease may be further divided into those where an initial surgical approach is unlikely to be successful in removal of all disease or to provide long-term local control and those with disease where a reasonable initial surgical approach is likely to achieve pathologically negative margins and provide long-term local control. Thus, stage IIIA patients are divided into those who have clinical T3N1M0 disease versus those who have clinical TanyN2M0 disease, based on evaluation by a multidisciplinary team. For patients with operable locally advanced disease, generally patients with clinical T3N1M0 disease, treatment is as outlined in BINV-1 through BINV-6.

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

Inoperable locally advanced breast cancer (clinical stage IIIA [except for T3N1M0], clinical stage IIIB, or clinical stage IIIC)

For patients with inoperable locally advanced disease at presentation, the initial use of anthracycline-based preoperative chemotherapy is standard therapy. Local therapy after preoperative therapy usually 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. If internal mammary lymph nodes are involved, they should also be irradiated. In the absence of detected internal mammary node involvement, consideration may be given to including the internal mammary lymph nodes in the RT field.

Patients with an inoperable stage III tumor with disease progression during preoperative chemotherapy should be considered for palliative breast irradiation in an attempt to enhance local control. In all subsets of patients, further systemic adjuvant chemotherapy after local therapy is felt to be standard. Tamoxifen (or an aromatase inhibitor if postmenopausal) should be added for those with hormone receptor-positive tumors or those with unknown hormone receptor status. Post-treatment follow-up for women with stage III disease is the same as for women with earlier-stage, invasive breast cancer.

Post-therapy Surveillance and Follow-up

Post-therapy follow-up is optimally performed by 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 after the completion of breast-conserving RT. The routine performance of alkaline phosphatase and liver function tests are not included in the Guidelines. In addition, the Panel notes no evidence to support the use of “tumor markers” for breast cancer, and routine bone scans, CT scans, MRI scans, PET scans, or ultrasound examinations in the asymptomatic patient provide no advantage in survival or ability to palliate recurrent disease and are, therefore, not recommended.

The use of dedicated breast MRI may be considered as an option for post-therapy surveillance and follow-up in women at high risk of bilateral disease, such as carriers of BRCA 1/2 mutations. Rates of contralateral breast cancer following either breast-conserving therapy or mastectomy have been reported to be increased in women with BRCA 1/2 mutations when compared with patients with sporadic breast cancer. The Panel recommends that women with intact uteri who are taking tamoxifen should have yearly gynecologic assessments and rapid
evaluation of any vaginal spotting that might occur because of the risk of tamoxifen-associated endometrial carcinoma in postmenopausal women\textsuperscript{181} (see BINV-15). The performance of routine endometrial biopsy or ultrasonography in the asymptomatic woman 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.

Symptom management for women on adjuvant endocrine therapies often requires treatment of hot flashes and the treatment of concurrent depression. Venlafaxine has specifically been studied and is an effective intervention in decreasing hot flashes.\textsuperscript{182} Recent evidence has suggested that concomitant use of tamoxifen with certain selective serotonin reuptake inhibitors (SSRIs) (eg, paroxetine and fluoxetine) may decrease plasma levels of endoxifen, an active metabolite of tamoxifen.\textsuperscript{183,184} These SSRIs may interfere with the enzymatic conversion of tamoxifen to endoxifen by inhibiting a particular isoform of cytochrome P-450 enzyme (CYP2D6) involved in the metabolism of tamoxifen. However, the SSRIs citalopram and venlafaxine appear to have only minimal effects on tamoxifen metabolism.

Premenopausal women who experience early ovarian failure secondary to adjuvant chemotherapy and postmenopausal women who are treated with an aromatase inhibitor are at increased risk for the development of osteopenia or osteoporosis with an associated increased risk of bone fracture. The guideline thus recommends monitoring of bone health during surveillance in these high risk women\textsuperscript{185} (see BINV-15).

A special situation arises in women who are premenopausal at diagnosis, who develop amenorrhea during or following treatment, and for whom the use of an aromatase inhibitor is considered. The continuation or return of ovarian function following chemotherapy with or without amenorrhea has been documented.\textsuperscript{148,149} If an aromatase inhibitor is considered in women with amenorrhea following treatment, baseline levels of estradiol and gonadotropin followed by serial monitoring of these hormones should be performed if endocrine therapy with an aromatase inhibitor is initiated.\textsuperscript{149} (see BINV-I). Bilateral oophorectomy assures postmenopausal status in young women with therapy-induced amenorrhea and may be considered prior to initiating therapy with an aromatase inhibitor in a young woman.

Follow-up also includes assessment of patient adherence to ongoing medication regimens such as endocrine therapies. Predictors of poor adherence to medication include the presence of side effects associated with the medication, and incomplete understanding by the patient of the benefits associated with regular administration of the medication.\textsuperscript{186} The Panel recommends the implementation of simple strategies to enhance patient adherence to endocrine therapy, such as direct questioning of the patient during office visits, as well as brief, clear explanations on the value of taking the medication regularly and the therapeutic importance of longer durations of endocrine therapy (see BINV-15).

**Stage IV Metastatic or Recurrent Breast Cancer**

The staging evaluation of women who present with metastatic or recurrent breast cancer includes history and physical exam, the performance of a CBC, platelet count, liver function tests, chest imaging, bone scan, radiographs of any long or weight-bearing bones that are painful or appear abnormal on bone scan, consideration of CT or MRI scan of the abdomen, biopsy documentation of first recurrence if possible, and determination of hormone receptor status (estrogen receptor and progesterone receptor) and HER2 status if not previously performed. Positron emission tomography (PET) scanning was added to the current guideline as an optional imaging procedure (category 2B). If performed, based on limited data, the Panel recommends that
PET scanning not replace the performance of other more established imaging studies.\textsuperscript{187}

**Local disease only**

Patients with local recurrence only are divided into those who had been treated initially 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 RT (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. Unresectable chest wall recurrent disease should be treated with RT if no prior RT has been given. Women whose disease recurs locally after initial breast-conserving therapy should undergo a total mastectomy. After local treatment, women with local recurrences should be considered for systemic chemotherapy or endocrine therapy.

The current Guidelines add, in the localized clinical scenarios of the treatment of recurrence/stage IV disease guideline (see BINV-16), the consideration of the addition of hyperthermia to irradiation for localized recurrences/metastasis (category 3). There have been several prospective randomized trials comparing RT to RT + hyperthermia in the treatment of locally advanced/recurrent cancers, primarily breast cancer chest wall recurrences.\textsuperscript{188,189} While there is heterogeneity among the study results, a recent series with strict quality assurance demonstrated a statistically significant increase in local tumor response and greater duration of local control with the addition of hyperthermia to radiation compared to radiation alone.\textsuperscript{189} No differences in overall survival have been demonstrated. Delivery of local hyperthermia is technically demanding and requires specialized expertise and equipment (eg, the monitoring of temperatures and management of possible tissue burns). The Panel thus recommends that the use of hyperthermia be limited to treatment centers with appropriate training, expertise, and equipment. The addition of hyperthermia generated substantial discussion and controversy among the Panel and is a category 3 recommendation.

**Systemic disease**

The treatment of systemic recurrence of breast cancer 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 endocrine therapies is preferred to the use of cytotoxic therapy whenever reasonable.

Women with bone metastasis, especially if lytic, should be given a bisphosphonate (eg, pamidronate or zoledronic acid) in combination with calcium citrate and vitamin D if expected survival is 3 months or longer and creatinine levels are below 3.0 mg/dL (category 1).\textsuperscript{185,190-195} Bisphosphonates are given in addition to chemotherapy or endocrine therapy. Zoledronic acid may be superior to pamidronate in lytic breast metastasis.\textsuperscript{196,197}

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

In postmenopausal women with previous antiestrogen therapy and who are within one year of antiestrogen exposure, recent evidence supports the use of a selective aromatase inhibitor as the preferred first-line therapy for their recurrent disease.\textsuperscript{198,199} For postmenopausal women who are antiestrogen naive or who are more than 1 year from previous antiestrogen therapy, the aromatase inhibitors appear to have superior outcome compared with tamoxifen, although the
differences are modest. Therefore, either tamoxifen or an aromatase inhibitor is an appropriate option in this setting.

In premenopausal women with previous antiestrogen therapy who are within 1 year of antiestrogen exposure, the preferred second-line therapy is either surgical or radiotherapeutic oophorectomy or leuteinizing hormone-releasing hormone (LHRH) agonists with or without an antiestrogen. In premenopausal women without previous exposure to an antiestrogen, initial treatment with an antiestrogen with or without a LHRH agonist is preferred.

Many premenopausal and postmenopausal women with hormone-responsive breast cancer benefit from sequential use of endocrine therapies at the time of disease progression. Therefore, women whose breast cancers respond to an endocrine maneuver with either shrinkage of the tumor or long-term disease stabilization (clinical benefit) should receive additional endocrine therapy at the time of disease progression. Additional endocrine therapies for second-line and subsequent therapy are listed in the endocrine algorithm (see BINV-J). The antiestrogen fulvestrant recently became available for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer previously treated with an antiestrogen. Fulvestrant lacks the estrogen agonistic activity of tamoxifen and is well tolerated as a single monthly gluteal intramuscular injection. Fulvestrant appears to be at least as effective as anastrozole in patients whose disease progressed on previous endocrine therapy, 206,207 and a recent reanalysis of these studies suggests a longer duration of response favoring fulvestrant. 208 Endocrine therapies in postmenopausal women include selective, nonsteroidal aromatase inhibitors (anastrozole and letrozole); steroidal aromatase inhibitors (exemestane); pure anti-estrogens (fulvestrant); progestin (megestrol acetate); androgens (fluoxymesterone); and high-dose estrogen (ethinyl estradiol). In premenopausal women, therapies include LHRH agonists (goserelin and luprolide); surgical or radiotherapeutic oophorectomy; progestin (megestrol acetate); androgens (fluoxymesterone); and high-dose estrogen (ethinyl estradiol). After second-line hormonal therapy, little high-level evidence exists to assist in selecting the optimal sequence of hormonal therapy.

Women with estrogen and progesterone receptor-negative tumors, symptomatic visceral metastasis, or endocrine therapy refractory disease should receive chemotherapy. A variety of chemotherapy regimens are felt to be appropriate, as outlined in the treatment algorithm (see BINV-K). Combination chemotherapy generally provides higher rates of objective response and longer time to progression, in comparison to single agent chemotherapy. Combination chemotherapy is, however, associated with an increase in toxicity, and is of little survival benefit. 209-212 Thus, the Panel finds little compelling evidence that combination chemotherapy is superior to sequential single agents. Standard clinical practice is to continue first-line chemotherapy until progression. Adverse effects may require dose reduction and cessation of chemotherapy prior to disease progression. Limited information suggests that progression-free survival can be prolonged with the use of continuous chemotherapy versus shorter course chemotherapy. 213,214 Due to the lack of overall survival differences, the use of prolonged versus shorter chemotherapy needs to be weighted against the detrimental effects of continuous chemotherapy on overall quality of life.

Preferred first-line chemotherapies thus include sequential single agents or combination chemotherapy. Among preferred first-line single agents, the Panel includes doxorubicin, epirubicin, pegylated liposomal doxorubicin, paclitaxel, docetaxel, capecitabine, vinorelbine (all category 2A), and gemcitabine (category 2B). Among preferred first-line combination regimens, the Panel includes cyclophosphamide, doxorubicin, and fluorouracil (FAC/CAF); fluorouracil, epirubicin, cyclophosphamide (FEC); doxorubicin, cyclophosphamide (AC);
epirubicin, cyclophosphamide (EC); doxorubicin in combination with either docetaxel or paclitaxel (AT); cyclophosphamide, methotrexate, fluorouracil (CMF); docetaxel, capecitabine; gemcitabine, paclitaxel. Other active agents include cisplatin, carboplatin, etoposide orally, vinblastine, and fluorouracil by continuous infusion. As with endocrine therapy, sequential responses are often observed with chemotherapy, supporting the use of sequential single agents and combination chemotherapy regimens. The current guideline includes doses and schedules of representative chemotherapy single agents and combination regimens for metastatic breast cancer (see BINV-K).

A recent trial randomized 715 women with recurrent or metastatic breast cancer to first-line chemotherapy with paclitaxel with or without bevacizumab, a humanized monoclonal antibody against the vascular endothelial growth factor (VEGF). This trial documented superior progression-free survival (hazard ratio 0.51; 95% CI 0.43-0.62; log rank test P <0.0001) favoring bevacizumab plus paclitaxel compared with paclitaxel alone. Improvements observed in overall survival with the addition of bevacizumab have not reached statistical significance.

Patients with tumors that are HER2-positive may derive benefit from treatment with trastuzumab as a single agent or in combination with selected chemotherapeutic agents. The Panel recommends selecting patients for trastuzumab therapy who have tumors either positive for HER2 by FISH or 3+ by IHC. HER2 testing recommendations are described in the guideline (see BINV-A). Patients with tumors IHC 0 or 1+ for HER2 or FISH not amplified have very low rates of trastuzumab response, and therapy with trastuzumab is not warranted. Adequate standardization and validation of HER2 assays used in clinical practice outside high-volume central facilities is a concern, and data suggest that false-positive determinations are common in low-volume testing facilities. In patients with metastatic or recurrent breast cancer with HER2-positive tumors, trastuzumab as a single agent or in combination with selected chemotherapeutics may be considered. A single randomized trial demonstrates benefit from adding trastuzumab to paclitaxel chemotherapy in patients with IHC 2+ or 3+ for HER2. Early nonrandomized 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 in the metastatic setting is too high for use of this combination outside the confines of a prospective clinical trial. The current guideline includes doses and schedules of representative chemotherapy single agents and regimens for use in combination with trastuzumab for metastatic breast cancer (see BINV-K).

Failure to achieve a tumor response to 3 sequential chemotherapy regimens or an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or greater was believed to be an indication for supportive therapy only (category 2B). 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 that may benefit from local irradiation, surgery, or regional chemotherapy (eg, intrathecal methotrexate for leptomeningeal carcinomatosis).
Paget’s Disease

Paget’s disease of the breast is a rare manifestation of breast cancer characterized by neoplastic cells in the epidermis of the nipple areolar complex. It most commonly presents with eczema of the areola, bleeding, ulceration, and itching of the nipple. The diagnosis is often delayed because of the rare nature of the condition and confusion with other dermatologic conditions. There is an associated cancer elsewhere in the breast in up to 80% of cases. The associated cancers are not necessarily located adjacent to the nipple areolar complex and may be either ductal carcinoma in situ (DCIS) or invasive cancer.

Women with clinical signs that raise suspicion for Paget’s disease require a complete history and physical examination and diagnostic breast imaging (see PAGET-1). If no other breast lesion is identified, breast MRI may be considered before or after biopsy of the nipple areolar complex. Any breast lesion identified by imaging or examination should be evaluated according to the NCCN Breast Screening and Diagnostic Guidelines. The skin of the nipple areolar complex should undergo surgical biopsy including the full thickness of the epidermis including at least a portion of any clinically involved nipple areolar complex.

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

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

For Paget’s disease without an associated cancer (ie, no palpable mass or imaging abnormality), it is recommended that breast-conserving surgery consist of removal of the entire nipple areolar complex with a negative margin of underlying breast tissue. In cases with an associated cancer elsewhere in the breast, the surgery includes removal of the nipple areolar complex with a negative margin, and removal of the peripheral cancer using standard breast-conserving technique to achieve a negative margin. It is not necessary to remove the nipple areolar complex and the peripheral cancer in continuity in a single surgical specimen or through a single incision. Mastectomy also remains an appropriate treatment option (see PAGET-2).

Axillary lymph node staging is not necessary for Paget’s disease without a detectable underlying cancer as this occurs predominantly in association with pure DCIS. In the presence of an underlying invasive breast cancer treated with breast-conserving surgery, axillary surgery should be performed according to the Surgical Axillary Staging guideline (see BINV-C). In cases treated by total mastectomy, sentinel node biopsy should be considered because the final pathology may reveal an invasive cancer in the mastectomy specimen and the mastectomy precludes subsequent sentinel node biopsy.

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

Women with an associated invasive cancer have substantial risk of developing metastases. Adjuvant systemic therapy should be administered according to the stage of the cancer. Women with Paget’s disease treated with breast conservation and without an associated cancer or those with associated DCIS should consider tamoxifen for risk reduction. Those with an associated invasive cancer should receive adjuvant systemic therapy based on the stage and hormone receptor status as outlined in BINV-4 to BINV-9.

Phyllodes tumors of the breast (also known as phylloides tumors, cystosarcoma phyllodes)

Phyllodes tumors of the breast are rare tumors comprised of both stromal and epithelial elements. Phyllodes tumors exist in benign, borderline, and malignant subtypes, although there is not uniform agreement on the criteria for assigning subtype or for predicting biological behavior. Subtype of phyllodes tumor appears less important for risk of recurrence than does the margin of tumor-free resection achieved by surgical treatment. Diagnosis of phyllodes tumors prior to excisional biopsy/lumpectomy is uncommon. Phyllodes tumors occur in an older age distribution than fibroadenoma, a younger age distribution than the invasive ductal and lobular cancers, and with a mean age in the 40’s. Phyllodes tumors often enlarge rapidly and are usually painless. Phyllodes tumors often appear on ultrasound and mammography as fibroadenomas, and fine needle aspiration cytology and even core needle biopsy are inadequate to reliably distinguish phyllodes tumors from fibroadenoma. Thus in the setting of a large or rapidly enlarging clinical fibroadenoma, excisional biopsy should be considered to pathologically exclude a phyllodes tumor. Patients with the Li-Fraumeni Syndrome (germ line p53 mutation, see NCCN Genetic/Familial High Risk Assessment Guidelines) have an increased risk of phyllodes tumors. Local recurrences of phyllodes tumors are the most common site of recurrence. Most distant recurrences occur in the lung, and may be solid nodules or thin-walled cavities.

Treatment of phyllodes tumors is with local surgical excision with tumor free margins of 1 cm or greater. Lumpectomy or partial mastectomy is the preferred surgical therapy. Total mastectomy is necessary only if negative margins cannot be obtained by lumpectomy or partial mastectomy (see PHYLL-1). Since phyllodes tumors rarely metastasize to the axillary lymph nodes, surgical axillary staging or axillary lymph node dissection is not necessary unless the lymph nodes are pathologic on clinical examination. In those patients who experience a local recurrence, resection of the recurrence with wide tumor-free surgical margins should be performed (see PHYLL-2). Some members of the Panel recommend local radiation therapy of the remaining breast or chest wall following resection of a local recurrence, but this recommendation is controversial (category 3).

While the epithelial component of most phyllodes tumors contains estrogen receptor (58%) and/or progesterone receptor (75%), endocrine therapy has no proven role in the treatment of phyllodes tumors. Similarly, there is no evidence that adjuvant cytotoxic chemotherapy provides benefit in reduction of recurrences or death. In the rare patient who experiences a systemic recurrence (usually in the lung), treatment should be as recommended in the NCCN Soft Tissue Sarcoma Guidelines.

Breast Cancer During Pregnancy

Breast cancer occurring concurrent with pregnancy is an infrequent clinical event. In a California registry study, there were 1.3 breast cancers diagnosed per 10,000 live births. Unfortunately, breast cancer during pregnancy is most often axillary lymph node-positive and
with larger primary tumor size. Histologically the tumors are poorly differentiated, more frequently estrogen and progesterone receptor-negative and approximately 30% are HER2-positive.235,236 The diagnosis is often delayed because neither the patient nor the physician suspects malignancy.

Evaluation of the pregnant patient with suspected breast cancer should include a physical examination with particular attention to the breast and regional lymph nodes. Mammogram of the breast with shielding can be done safely and the accuracy is reported to be greater than 80%.237 Ultrasound of the breast and regional lymph nodes can be used to assess the extent of disease and also to guide biopsy. Ultrasound has been reported to be abnormal in up to 100% of breast cancers occurring during pregnancy.237 Biopsies for cytologic evaluation of a suspicious breast mass may be done with a fine needle aspiration (FNA) of the breast and suspicious lymph nodes. However, the preferred technique is core needle biopsy. This provides tissue for histologic confirmation of invasive disease as well as providing adequate tissue for hormone receptor and HER2 analyses.

Staging assessment of the pregnant patient with breast cancer may be guided by clinical disease stage. For clinically node-negative T1-T2 tumors, a chest x-ray (with shielding), liver function and renal function assessment and complete blood count with differential is appropriate. In patients who have clinically node-positive or T3 breast lesions, in addition to the aforementioned, an ultrasound of the liver and consideration of a screening MRI of the thoracic and lumbar spine without contrast may be employed. The documentation of the presence of metastases may alter the treatment plan and influence the patient’s decision regarding maintenance of the pregnancy.

Assessment of the pregnancy should include a maternal fetal medicine consultation and review of antecedent maternal risks such as hypertension, diabetes and complications with prior pregnancies. Documentation of fetal growth and development and fetal age by means of ultrasonographic assessment is appropriate. Estimation of the date of the delivery will help with systemic chemotherapy planning. In addition, maternal fetal medicine consultation should include counseling regarding maintaining or terminating pregnancy. Counseling of the pregnant patient with breast cancer should include a review of the treatment options which include mastectomy or breast-conserving surgery as well as the use of systemic therapy. The most common surgical procedure has been modified radical mastectomy. However, Kuerer et al. have shown that breast-conserving surgery is possible if radiation therapy can be delayed to the postpartum period.238

Sentinel lymph node biopsy with radioactive tracer (eg, technectium 99m sulfur colloid) should be safe. There are limited data with only case reports and estimations of fetal radiation dose.239,240 Isosulfan blue dye for sentinel node biopsy procedures is not recommended during pregnancy.

The indications for systemic chemotherapy are the same in the pregnant patient as in the non-pregnant breast cancer patient, although chemotherapy should not be administered at any point during the first trimester of pregnancy. The greatest experience in pregnancy has been with anthracycline and alkylating agent chemotherapy.241,242 Collected data of chemotherapy exposure in utero indicates that the first trimester has the greatest risk of fetal malformation.243,244 Fetal malformation risks in the second and third trimester are approximately 1.3%, not different than that of fetuses not exposed to chemotherapy during pregnancy. If systemic therapy is initiated, fetal monitoring prior to each chemotherapy cycle is appropriate. Chemotherapy during pregnancy should not be given after week 35 of pregnancy in order to avoid the potential for hematologic complications at the time of delivery. Recent data from a single institution prospective study indicate that FAC chemotherapy (5-FU 500 mg/m² IV day 1 and 4, doxorubicin 50 mg/m²
by IV infusion over 72 hours and cyclophosphamide 500 mg/m² IV day 1) may be given with relative safety during the second and third trimesters of pregnancy.\textsuperscript{242} Ondansetron, lorazepam and dexamethasone can be used as part of the pre-chemotherapy antiemetic regimen. As reported by Gwyn et al., the median gestational age at delivery was 38 weeks, more than 50% of the patients had vaginal delivery and there have been no fetal deaths.

There are limited data on the use of taxanes during pregnancy.\textsuperscript{245} As a consequence they are not recommended for use during pregnancy. If taxane use is indicated clinically, it may be used in the post-delivery setting.

There are only two case reports of trastuzumab use during pregnancy.\textsuperscript{246,247} Both case reports indicated oligohydramnios with administration of trastuzumab. If trastuzumab is otherwise indicated, it should be administered in the postpartum period.

Endocrine therapy and radiation therapy are contraindicated during pregnancy. Endocrine therapy and radiation therapy, if indicated, should thus not be initiated until the post-partum period.

Communication between the oncologist and maternal fetal medicine specialist is essential at every visit and treatment decision point for the patient (see PREG-1).

Summary

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

With rare exceptions, the evaluation, treatment, and follow-up recommendations in these Guidelines are based 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/physician participation in prospective clinical trials allows patients to not only receive state-of-the-art cancer treatment but also to contribute to improving the treatment of future patients.

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