NCCN

National
Comprehensive
Cancer
Network

Clinical Practice Guidelines in Oncology – v.2.2005

Breast Cancer

Version 2.2005

We Need Your Feedback!

Continue

NCCN Breast Cancer Panel Members

* **Robert W. Carlson, MD/Chair**
Stanford Hospital and Clinics

Benjamin O. Anderson, MD
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

Harold J. Burstein, MD, PhD
Dana-Farber/Partners CancerCare

W. Bradford Carter, MD
H. Lee Moffitt Cancer Center & Research
Institute at the University of South Florida

* **Stephen B. Edge, MD**
Roswell Park Cancer Institute

William B. Farrar, MD
Arthur G. James Cancer Hospital & Richard
J. Solove Research Institute at The Ohio
State University

Lori J. Goldstein, MD
Fox Chase Cancer Center

William J. Gradishar, MD
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Daniel F. Hayes, MD
University of Michigan Comprehensive
Cancer Center

Clifford Hudis, MD
Memorial Sloan-Kettering Cancer Center

Mohammad Jahanzeb, MD
St. Jude Children's Research Hospital/
University of Tennessee Cancer Institute

Britt-Marie Ljung, MD
UCSF Comprehensive Cancer Center

Lawrence B. Marks, MD
Duke Comprehensive Cancer Center

* **Beryl McCormick, MD**
Memorial Sloan-Kettering Cancer Center

Lisle M. Nabell, MD
University of Alabama at Birmingham
Comprehensive Cancer Center

Lori J. Pierce, MD
University of Michigan Comprehensive
Cancer Center

Elizabeth C. Reed, MD
UNMC Eppley Cancer Center at The
Nebraska Medical Center

Samuel M. Silver, MD, PhD
University of Michigan Comprehensive
Cancer Center

Mary Lou Smith, JD, MBA
Consultant

George Somlo, MD
City of Hope Cancer Center

* **Richard Theriault, DO, MBA**
The University of Texas M. D. Anderson
Cancer Center

John H. Ward, MD
Huntsman Cancer Institute at the
University of Utah

Eric P. Winer, MD
Dana-Farber/Partners CancerCare

Antonio C. Wolff, MD
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins
University

Continue

* Writing Committee member

Table of Contents

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

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

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

See NCCN Categories of Consensus

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2005.

DIAGNOSIS **WORKUP** **PRIMARY TREATMENT** **RISK REDUCTION** **SURVEILLANCE/FOLLOW-UP**

Lobular carcinoma in situ (LCIS) Stage 0 Tis, N0, M0[a]

→

- **H&P**
- **Diagnostic bilateral mammogram**
- **Pathology review**[b]

→ **Observation** →

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

→

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

[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. http://www.cap.org/apps/docs/cancer_protocols/protocols_index.html

Return to Breast Cancer Guideline Table of Contents

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.

NCCN®

**Practice Guidelines
in Oncology – v.2.2005**

Ductal Carcinoma *In Situ*

Guidelines Index
Breast Cancer TOC
Staging, MS, References

DIAGNOSIS

WORKUP

FINDINGS

**Ductal carcinoma
in situ (DCIS)
Stage 0
Tis, N0, M0**[a]

→

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

Widespread disease (2 or more quadrants)

Excisional biopsy[b]

Margins positive[c,d]

→ **See Primary Treatment (DCIS-2)**

Margins negative[c,d]

---

[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. http://www.cap.org/apps/docs/cancer_protocols/protocols_index.html

[c]Re-resection(s) may be performed in an effort to obtain negative margins in patients desiring breast conserving therapy. Patients not amenable to margin-free excision should have total mastectomy.
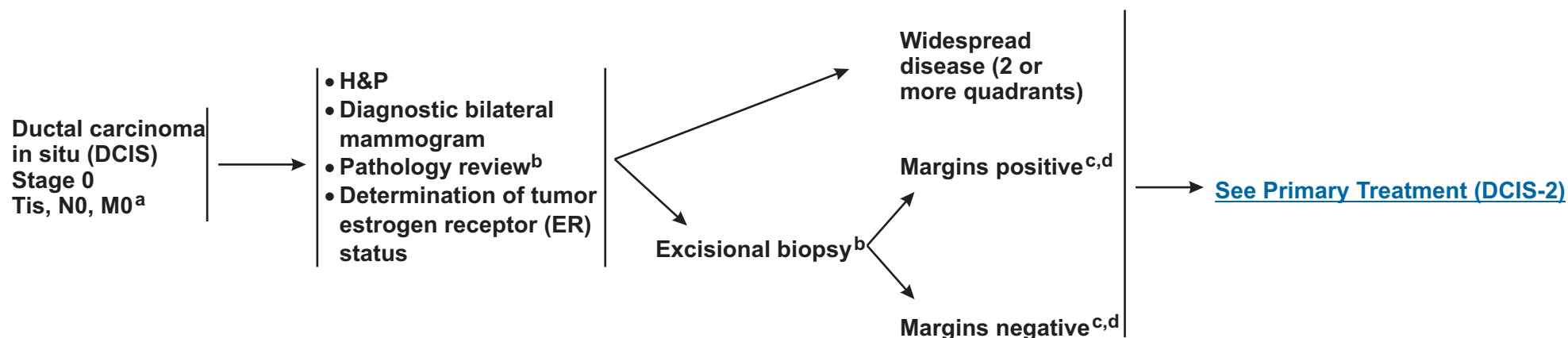
[d]See margin status in DCIS (DCIS-A).

**Return to Breast
Cancer Guideline
Table of Contents**

> **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.**

DCIS-1

FINDINGS

PRIMARY TREATMENT

Widespread disease (2 or more quadrants) → **Total mastectomy without lymph node dissection**[h,k] **± reconstruction** →

Margins positive[c] →

Excision[k] **+ RT** [e,f,g,h,i]
or
Total mastectomy without lymph node dissection[f,h,k] **± reconstruction** →

See Postsurgical Treatment (DCIS-3)

Margins negative[c,d] →

Small (< 0.5 cm), unicentric, low grade →

Excision[k] **+ RT** [e,f,g,h,i,j]
or
Total mastectomy without lymph node dissection[f,h,k] **± reconstruction**
or
Excision alone (category 2B)[g,h,i,j,k]

→

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

[d]See margin status in DCIS (DCIS-A).

[e]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. There is no role for partial breast irradiation outside a therapeutic clinical trial.

[f]Long-term survival with mastectomy versus excision and irradiation appears to be equivalent.

[g]Complete resection should be documented by analysis of margins, specimen mammography and where appropriate post-excision mammography.

[h]Patients found to have invasive disease at total mastectomy or re-excision should be managed as stage I or stage II disease, including lymph node staging.

[i]See Contraindications to Breast-Conserving Therapy (BINV-D).

[j]Prospective studies have demonstrated that whole breast radiation lowers the risk of ipsilateral invasive breast cancer recurrence following excision of DCIS. Some patients may be treated with excision alone, particularly if a patient is willing to accept a higher risk of local recurrence. Other factors that should be considered include patient age, comorbidity, tumor margins and tumor grade.

[k]Axillary lymph node staging is discouraged in women with apparent pure DCIS. However, a small proportion of patients with apparent pure DCIS will be found to have invasive cancer at the time of their definitive surgical procedure. Therefore, the performance of a sentinel lymph node procedure may be considered if the patient with apparent pure DCIS is to be treated with mastectomy or with excision in an anatomic location compromising the performance of a future sentinel lymph node procedure.

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.

DCIS POSTSURGICAL TREATMENT

SURVEILLANCE/FOLLOW-UP

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

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

→

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

[l]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).

Return to Breast Cancer Guideline Table of Contents

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.

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. There are insufficient data to make definitive statements regarding margins between 1 and 10 mm.

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.

DCIS-A

CLINICAL STAGE   **WORKUP**

Stage I
  T1, N0, M0
or
Stage IIA
  T0, N1, M0
  T1, N1, M0
  T2, N0, M0
or
Stage IIB
  T2, N1, M0
  T3, N0, M0
or
  T3, N1, M0

- **H&P**
- **CBC, platelets**
- **Liver function tests**
- **Chest x-ray**
- **Diagnostic bilateral mammogram, ultrasound as necessary**
- **Pathology review[a]**
- **Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER-2 status[b]**
- **Breast MRI with dedicated breast coil may be considered for breast conserving therapy for preoperative evaluation of extent of disease and detection of mammographically occult disease in the breast (optional). Decision making regarding breast conservation should not be made on the basis of MRI imaging alone in the absence of tissue sampling.**
- **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, or if T3, N1, M0) (category 2B)**

See Locoregional Treatment (BINV-2)

[a]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
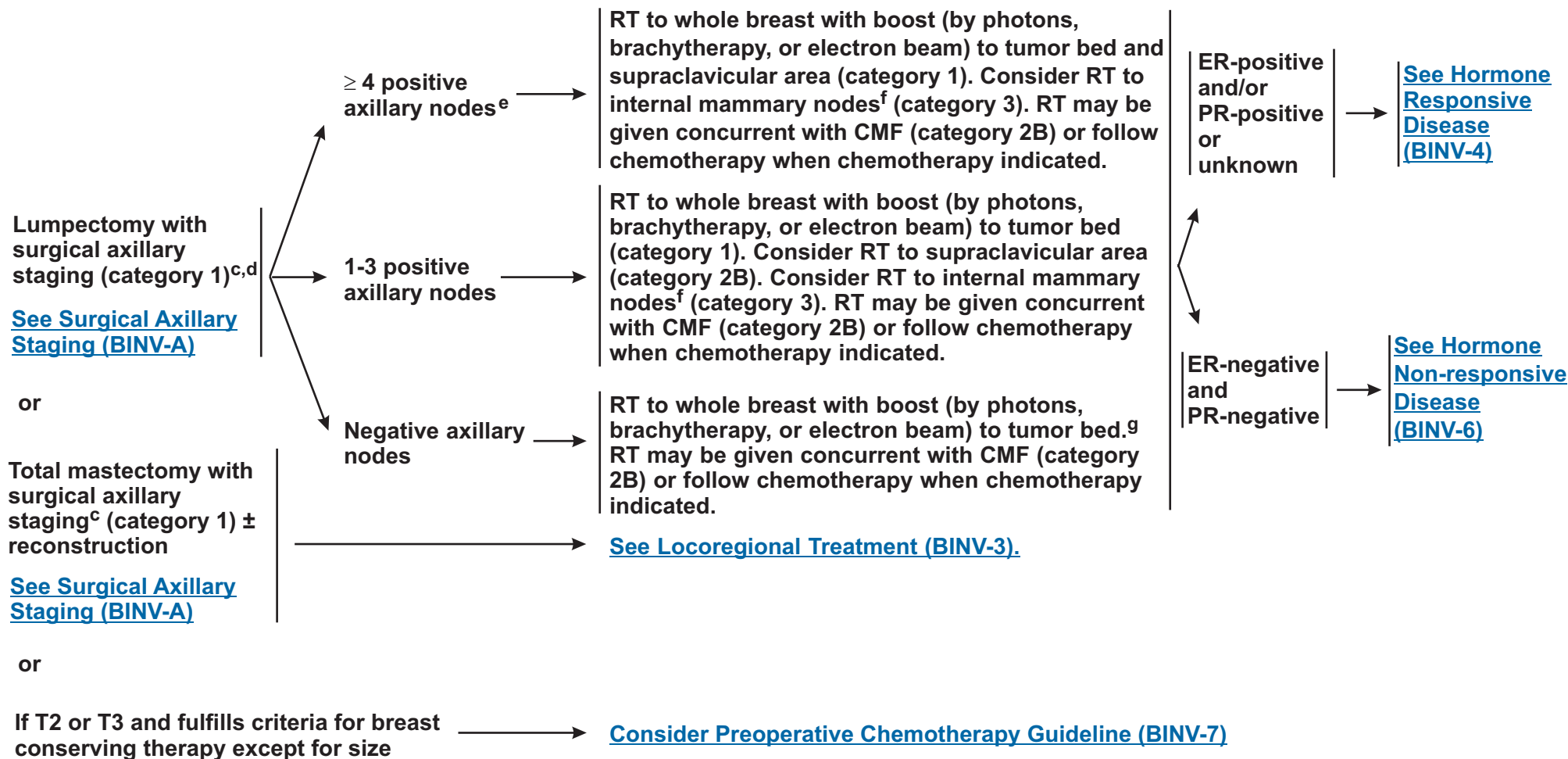[b]HER-2 testing should be done using IHC and/or FISH. An IHC result of 2+ should be confirmed by FISH.

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

BINV-1

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

Lumpectomy with surgical axillary staging (category 1)[c,d]

See Surgical Axillary Staging (BINV-A)

or

Total mastectomy with surgical axillary staging[c] (category 1) ± reconstruction

See Surgical Axillary Staging (BINV-A)

→ **≥ 4 positive axillary nodes[e]** → RT to whole breast with boost (by photons, brachytherapy, or electron beam) to tumor bed and supraclavicular area (category 1). Consider RT to internal mammary nodes[f] (category 3). RT may be given concurrent with CMF (category 2B) or follow chemotherapy when chemotherapy indicated.

→ **1-3 positive axillary nodes** → RT to whole breast with boost (by photons, brachytherapy, or electron beam) to tumor bed (category 1). Consider RT to supraclavicular area (category 2B). Consider RT to internal mammary nodes[f] (category 3). RT may be given concurrent with CMF (category 2B) or follow chemotherapy when chemotherapy indicated.

→ **Negative axillary nodes** → RT to whole breast with boost (by photons, brachytherapy, or electron beam) to tumor bed.[g] RT may be given concurrent with CMF (category 2B) or follow chemotherapy when chemotherapy indicated.

ER-positive and/or PR-positive or unknown → **See Hormone Responsive Disease (BINV-4)**

ER-negative and PR-negative → **See Hormone Non-responsive Disease (BINV-6)**

→ **See Locoregional Treatment (BINV-3).**

or

If T2 or T3 and fulfills criteria for breast conserving therapy except for size → **Consider Preoperative Chemotherapy Guideline (BINV-7)**

[c]See Axillary Dissection (BINV-B) and Margin Status in Infiltrating Carcinoma (BINV-C).
[d]See Contraindications to Breast-Conserving Therapy (BINV-D).
[e]Consideration may be given to additional staging including bone scan and abdominal CT/US/MRI; chest CT (category 2B).
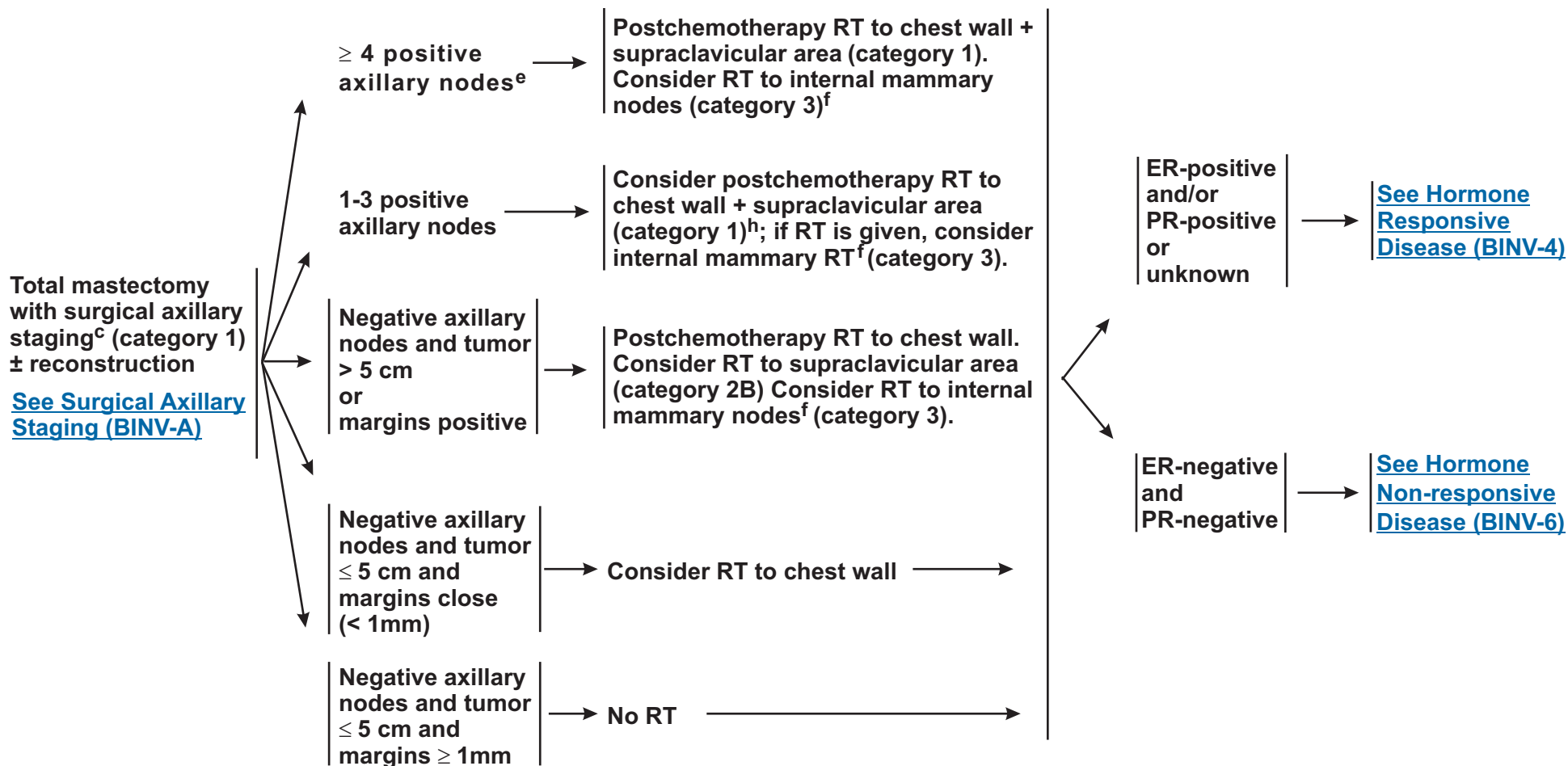[f]RT should be given to the internal mammary lymph nodes if they are clinically or pathologically positive, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be utilized in all cases where RT is delivered to the internal mammary lymph nodes.
[g]Breast irradiation may be omitted in those 70 y of age or older with estrogen-receptor positive, clinically node negative, T1 tumors who receive adjuvant hormonal therapy (category 1).

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.

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

Total mastectomy with surgical axillary staging[c] (category 1) ± reconstruction

See Surgical Axillary Staging (BINV-A)

→ **≥ 4 positive axillary nodes[e]** → Postchemotherapy RT to chest wall + supraclavicular area (category 1). Consider RT to internal mammary nodes (category 3)[f]

→ **1-3 positive axillary nodes** → Consider postchemotherapy RT to chest wall + supraclavicular area (category 1)[h]; if RT is given, consider internal mammary RT[f] (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[f] (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 →

→ **ER-positive and/or PR-positive or unknown** → **See Hormone Responsive Disease (BINV-4)**

→ **ER-negative and PR-negative** → **See Hormone Non-responsive Disease (BINV-6)**

[c]See Axillary Dissection (BINV-B) and Margin Status in Infiltrating Carcinoma (BINV-C).
[e]Consideration may be given to additional staging including bone scan; abdominal CT/US/MRI; chest CT (category 2B).
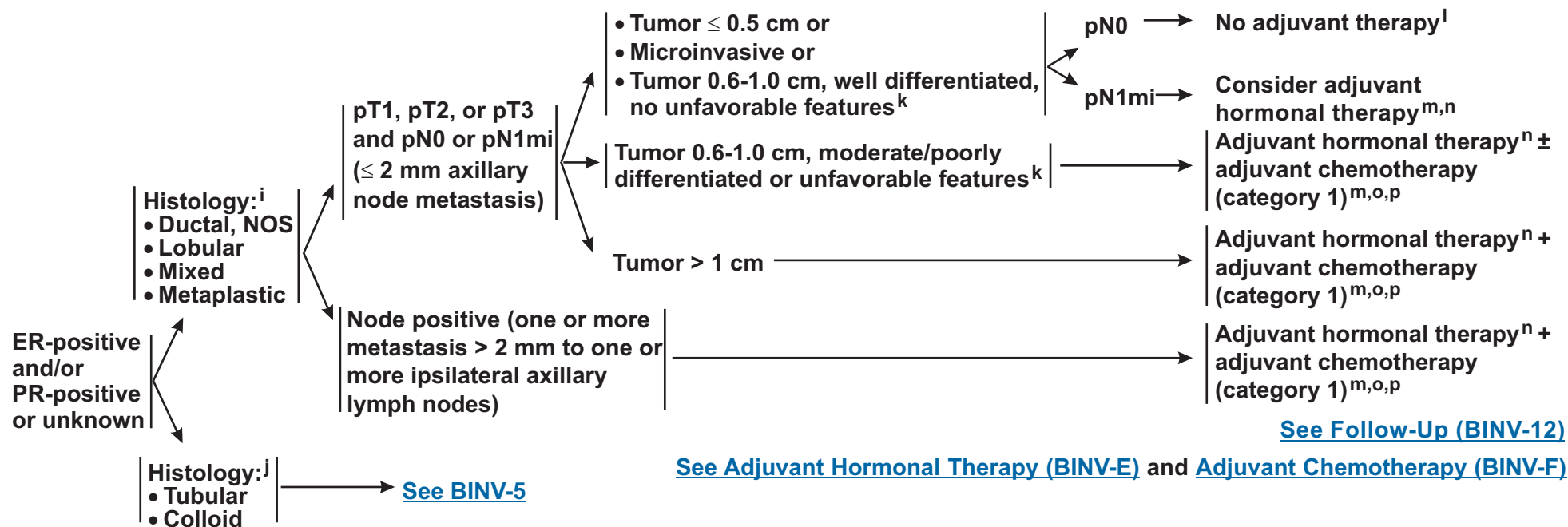[f]RT should be given to the internal mammary lymph nodes that are clinically or pathologically positive, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be utilized in all cases where RT is delivered to the internal mammary lymph nodes.
[h] 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.

SYSTEMIC ADJUVANT TREATMENT - HORMONE RESPONSIVE DISEASE

ER-positive and/or PR-positive or unknown

Histology:[i]
- Ductal, NOS
- Lobular
- Mixed
- Metaplastic

pT1, pT2, or pT3 and pN0 or pN1mi ($\leq$ 2 mm axillary node metastasis)

- Tumor $\leq$ 0.5 cm or
- Microinvasive or
- Tumor 0.6-1.0 cm, well differentiated, no unfavorable features[k]

→ pN0 → **No adjuvant therapy[l]**

→ pN1mi → **Consider adjuvant hormonal therapy[m,n]**

Tumor 0.6-1.0 cm, moderate/poorly differentiated or unfavorable features[k] → **Adjuvant hormonal therapy[n] ± adjuvant chemotherapy (category 1)[m,o,p]**

Tumor > 1 cm → **Adjuvant hormonal therapy[n] + adjuvant chemotherapy (category 1)[m,o,p]**

Node positive (one or more metastasis > 2 mm to one or more ipsilateral axillary lymph nodes) → **Adjuvant hormonal therapy[n] + adjuvant chemotherapy (category 1)[m,o,p]**

See Follow-Up (BINV-12)

See Adjuvant Hormonal Therapy (BINV-E) and Adjuvant Chemotherapy (BINV-F)

Histology:[j]
- Tubular
- Colloid

→ **See BINV-5**

---

[i] 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.

[j] See text paragraph for medullary carcinoma (MS-13).

[k] Unfavorable features: angiolymphatic invasion, high nuclear grade, high histologic grade, HER-2 overexpression (category 2B).

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

[m] 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 (ie, 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.
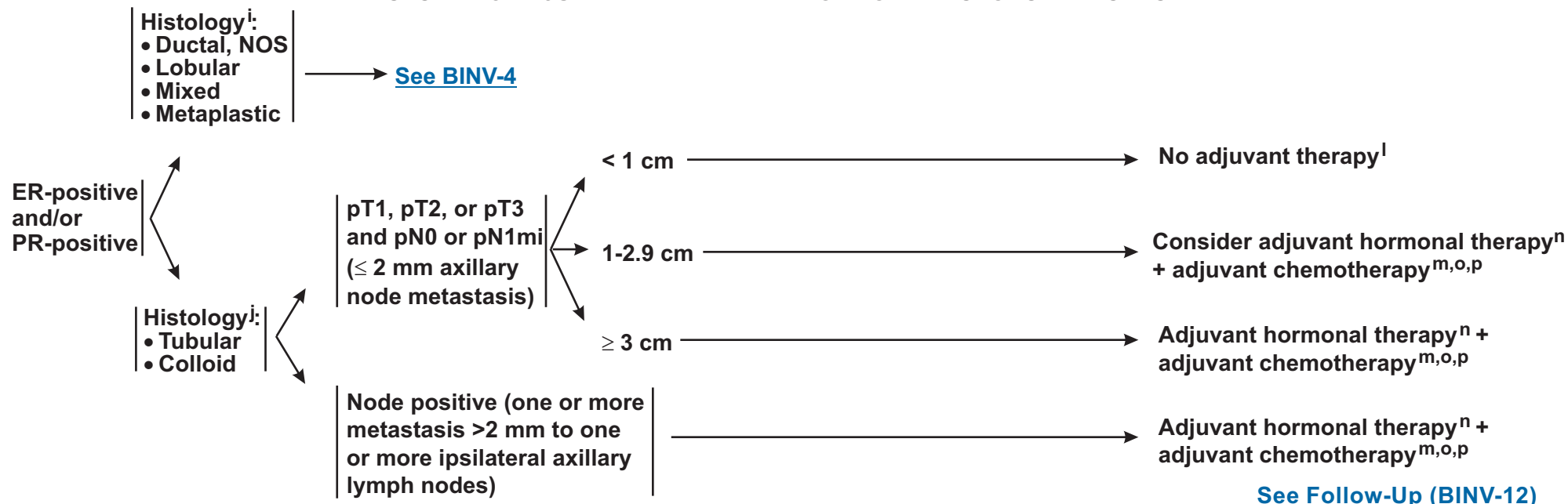
[n] See Adjuvant Hormonal Therapy (BINV-E).

[o] 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 $\geq$ 60 y where the incremental benefit of chemotherapy may be smaller. Available data suggest sequential or concurrent hormonal therapy with RT is acceptable.

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

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 RESPONSIVE DISEASE

Histology[i]:
- Ductal, NOS
- Lobular
- Mixed
- Metaplastic

→ **See BINV-4**

ER-positive and/or PR-positive

Histology[j]:
- Tubular
- Colloid

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

- **< 1 cm** ⟶ **No adjuvant therapy[l]**
- **1-2.9 cm** ⟶ **Consider adjuvant hormonal therapy[n] + adjuvant chemotherapy[m,o,p]**
- **≥ 3 cm** ⟶ **Adjuvant hormonal therapy[n] + adjuvant chemotherapy[m,o,p]**

Node positive (one or more metastasis >2 mm to one or more ipsilateral axillary lymph nodes) ⟶ **Adjuvant hormonal therapy[n] + adjuvant chemotherapy[m,o,p]**

See Follow-Up (BINV-12)

See Adjuvant Hormonal Therapy (BINV-E) and **Adjuvant Chemotherapy (BINV-F)**

[i] 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.

[j] See text paragraph for medullary carcinoma (MS-13).

[k] Unfavorable features: angiolymphatic invasion, high nuclear grade, high histologic grade, HER-2 overexpression (category 2B).

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

[m] 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 (ie, 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.
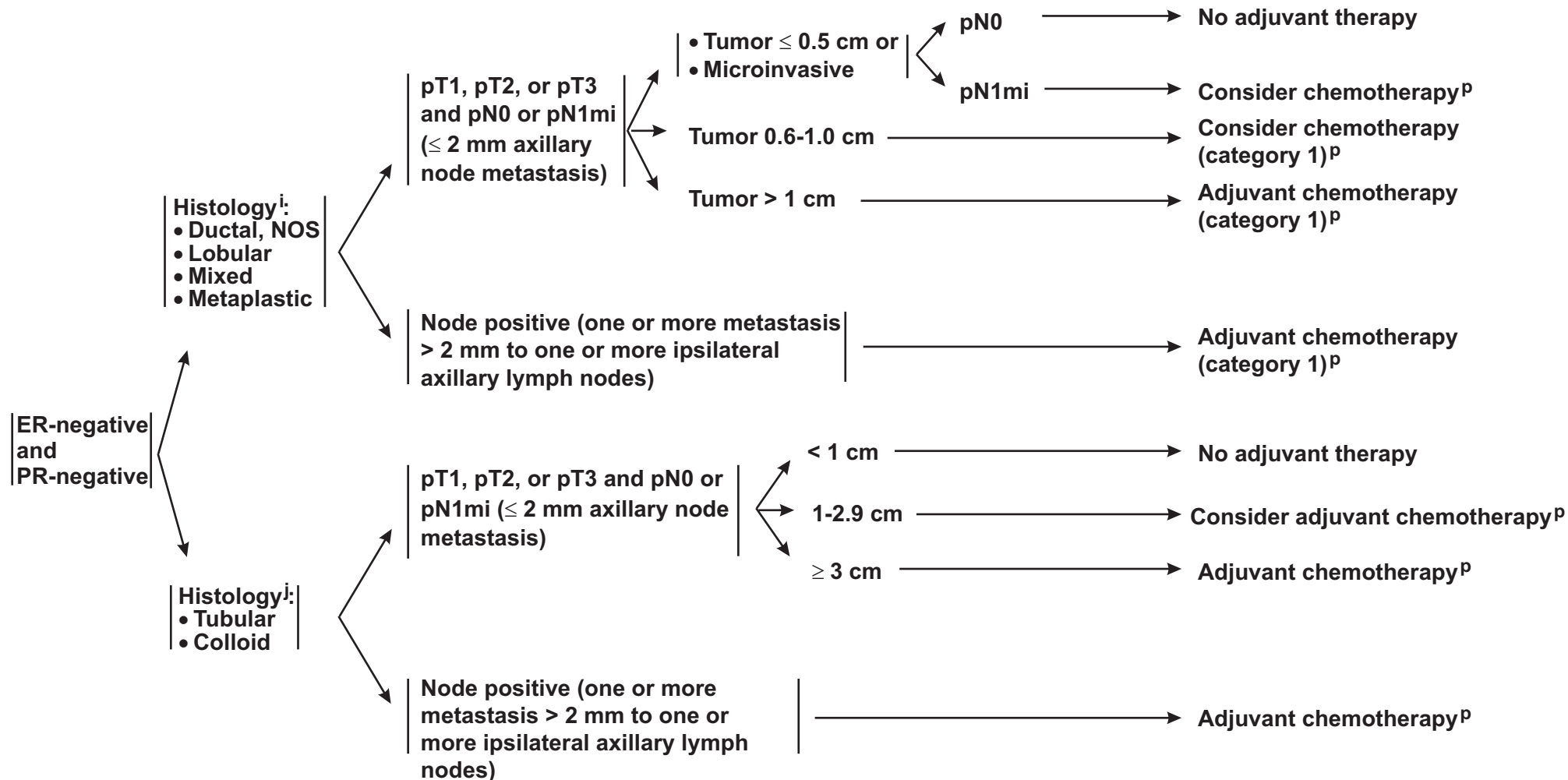
[n] See Adjuvant Hormonal Therapy (BINV-E).

[o] 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.

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

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 NON-RESPONSIVE DISEASE

ER-negative and PR-negative

Histology[i]:
- **Ductal, NOS**
- **Lobular**
- **Mixed**
- **Metaplastic**

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

- **Tumor ≤ 0.5 cm or**
- **Microinvasive**

- **pN0** → No adjuvant therapy
- **pN1mi** → Consider chemotherapy[p]

Tumor 0.6-1.0 cm → Consider chemotherapy (category 1)[p]

Tumor > 1 cm → Adjuvant chemotherapy (category 1)[p]

Node positive (one or more metastasis > 2 mm to one or more ipsilateral axillary lymph nodes) → Adjuvant chemotherapy (category 1)[p]

Histology[j]:
- **Tubular**
- **Colloid**

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

- **< 1 cm** → No adjuvant therapy
- **1-2.9 cm** → Consider adjuvant chemotherapy[p]
- **≥ 3 cm** → Adjuvant chemotherapy[p]

Node positive (one or more metastasis > 2 mm to one or more ipsilateral axillary lymph nodes) → Adjuvant chemotherapy[p]

[i]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.

[j]See text paragraph for medullary carcinoma (MS-13).

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

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

BINV-6

NCCN®

**Practice Guidelines
in Oncology – v.2.2005**

Invasive Breast Cancer

Guidelines Index
Breast Cancer TOC
Staging, MS, References

Preoperative Chemotherapy Guideline

CLINICAL STAGE

WORKUP

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

- **H&P**
- **CBC, platelets**
- **Liver function tests**
- **Chest x-ray**
- **Diagnostic bilateral mammogram, ultrasound as necessary**
- **Pathology review**
- **Determination of tumor ER/PR status and HER-2 status[b]**
- **Breast MRI with dedicated breast coil may be considered for breast conserving therapy for preoperative evaluation of extent of disease and detection of mammographically occult disease in the breast (optional). Decision making regarding breast conservation should not be made on the basis of MRI imaging alone in the absence of tissue sampling.**
- **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, or if T3, N1, M0) (category 2B)**

**See Primary
Treatment
(BINV-8)**

[b]HER-2 testing should be done using IHC and/or FISH. An IHC result of 2+ should be confirmed by FISH.

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

BINV-7

NCCN®

**Practice Guidelines
in Oncology – v.2.2005**

Invasive Breast Cancer

Guidelines Index
Breast Cancer TOC
Staging, MS, References

Preoperative Chemotherapy Guideline

PRIMARY TREATMENT

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)
See Surgical Axillary Staging (BINV-A) →

Localization of tumor bed for future surgical management →

Preoperative chemotherapy^q (Hormonal therapy alone may be considered for receptor positive disease in postmenopausal patients)^r →

No response after 3-4 cycles or Progressive disease^q →

Partial response, lumpectomy not possible →

Consider alternative chemotherapy →

No response after 3-4 cycles or Progressive disease^q →

Partial response, lumpectomy not possible →

See Mastectomy pathway (BINV-9)

Partial response, lumpectomy possible or Complete response →

See Lumpectomy pathway (BINV-9)

Does not desire breast preservation → **See Stage I and II breast cancer (BINV-1 and BINV-2)**

^{q}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-F) may be considered in the preoperative setting. If treated with hormonal therapy, an aromatase inhibitor is preferred for postmenopausal women.

^{r}Definition of Menopause (See BINV-G).

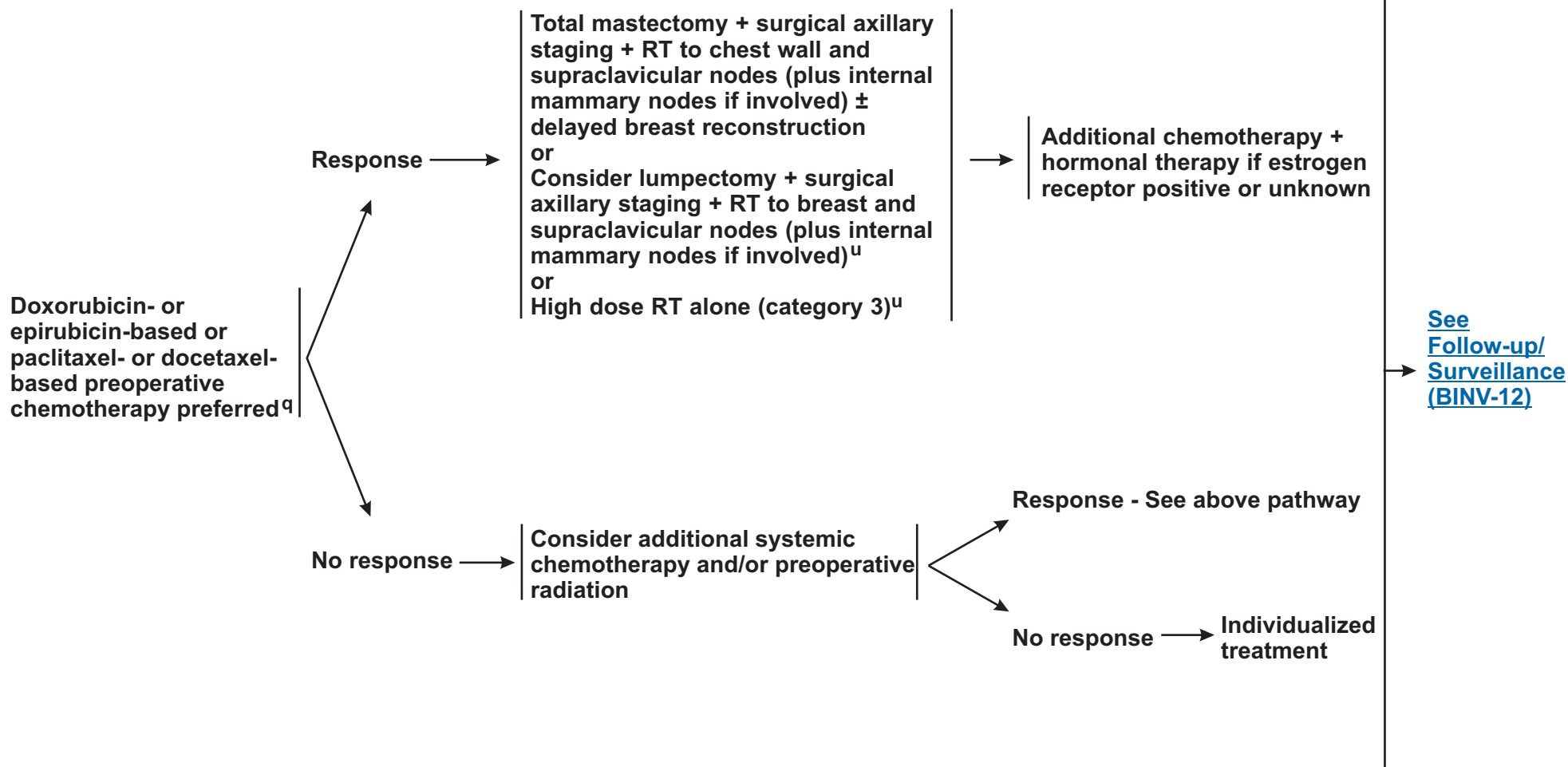> **Note: All recommendations are category 2A unless otherwise indicated.**
> **Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.**

Preoperative Chemotherapy Guideline

PRIMARY TREATMENT

ADJUVANT TREATMENT

Mastectomy and surgical axillary staging[s] ± reconstruction. If sentinel lymph node biopsy performed prechemotherapy and negative findings, may omit axillary lymph node dissection

→ **Consider additional chemotherapy** →

- **Adjuvant RT post-mastectomy is based on prechemotherapy tumor characteristics as per BINV-3[t]**
  and
- **Hormonal therapy if ER-positive (category 1)[n,o]**

See Adjuvant Hormonal Therapy (BINV-E)

Lumpectomy with surgical axillary staging.[s] If sentinel lymph node biopsy performed prechemotherapy and negative findings, may omit axillary lymph node dissection

→ **Consider additional chemotherapy** →

- **Adjuvant RT post-lumpectomy based on prechemotherapy tumor characteristics as per BINV-2[t]**
  and
- **Hormonal therapy if ER-positive (category 1)[n,o]**

See Adjuvant Hormonal Therapy (BINV-E)

→ **See Surveillance/ Follow-up (BINV-12)**

---

[n]See Adjuvant Hormonal Therapy (BINV-E).

[o]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.

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

[t]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

WORKUP

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

(Stage IIIA patients with T3, N1, M0 disease, see BINV-1)

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

Stage IIIC
  Any T, N3, M0

- **H&P**
- **CBC, platelets**
- **Liver function tests**
- **Chest CT scan (category 2B) ± chest x-ray**
- **Pathology review**
- **Prechemotherapy determination of tumor ER/PR receptor status and HER-2 status [b]**
- **Diagnostic bilateral mammogram, ultrasound as necessary**
- **Bone scan (category 2B)**
- **Abdominal CT or US or MRI (category 2B)**
- **Breast MRI with dedicated breast coil may be considered for breast conserving therapy for preoperative evaluation of extent of disease and detection of mammographically occult disease in the breast (optional). Decision making regarding breast conservation should not be made on the basis of MRI imaging alone in the absence of tissue sampling.**

See Preoperative Chemotherapy and Locoregional Treatment (BINV-11)

Stage IV
  any T, any N, M1

See Initial Workup for Stage IV Disease (BINV-12)

Return to Breast Cancer Guideline Table of Contents

[b]HER-2 testing should be done using IHC and/or FISH. An IHC result of 2+ should be confirmed by FISH.

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 FOR LOCALLY ADVANCED INVASIVE BREAST CANCER

LOCOREGIONAL TREATMENT

ADJUVANT TREATMENT

Doxorubicin- or epirubicin-based or paclitaxel- or docetaxel-based preoperative chemotherapy preferred[q]

Response ⟶

Total mastectomy + surgical axillary staging + RT to chest wall and supraclavicular nodes (plus internal mammary nodes if involved) ± delayed breast reconstruction
or
Consider lumpectomy + surgical axillary staging + RT to breast and supraclavicular nodes (plus internal mammary nodes if involved)[u]
or
High dose RT alone (category 3)[u]

⟶ Additional chemotherapy + hormonal therapy if estrogen receptor positive or unknown

See Follow-up/ Surveillance (BINV-12)

No response ⟶ Consider additional systemic chemotherapy and/or preoperative radiation

⟶ **Response - See above pathway**

No response ⟶ Individualized treatment

---

[q] 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-F) may be considered in the preoperative setting. If treated with hormonal therapy, an aromatase inhibitor is preferred for postmenopausal women.
[u] There are no data regarding breast conserving surgery in the management of inflammatory breast cancer.

Return to Breast Cancer Guideline Table of Contents

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

BINV-11

SURVEILLANCE/FOLLOW-UP

RECURRENCE WORKUP
or
INITIAL WORKUP FOR STAGE IV DISEASE

- 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: pelvic exam 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

→

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

Local disease only

Systemic disease[v]

→ **See Treatment of Recurrence/ Stage IV Disease (BINV-13)**

[b]HER-2 testing should be done using IHC and/or FISH. An IHC result of 2+ should be confirmed by FISH.
[v]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 $\geq$ 3 months, and creatinine < 3.0 mg/dL.

Return to Breast Cancer Guideline Table of Contents

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.

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**

Systemic disease[v]

→ **ER/PR positive or bone/soft tissue only or asymptomatic visceral**
- → **Prior antiestrogen within 1 y** → **Second-line hormonal therapy[w]** → See (BINV-14)
- → **No prior antiestrogen or > 1 y off antiestrogen**
  - → **Postmenopausal[r]** → **Aromatase inhibitor or Antiestrogen** → See (BINV-14)
  - → **Premenopausal[r]** → **Ovarian ablation or suppression, plus hormonal therapy as for postmenopausal women or Antiestrogen** → See (BINV-14)

→ **ER/PR negative or symptomatic visceral or hormone refractory**
- → **HER-2[b] over-expressed** → **Trastuzumab ± chemotherapy[x,y,z]** → **No response to 3 sequential regimens or ECOG performance status ≥ 3** → **Consider no further cytotoxic therapy. See NCCN Palliative Care Guidelines**
- → **HER-2[b] not over-expressed** → **Chemotherapy[x]** → **No response to 3 sequential regimens or ECOG performance status ≥ 3** → **Consider no further cytotoxic therapy. See NCCN Palliative Care Guidelines**

TREATMENT OF RECURRENCE

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

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

---

[b]HER-2 testing should be done using IHC and/or FISH. An IHC result of 2+ should be confirmed by FISH.

[r]Definition of Menopause (See BINV-G).

[v]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.

[w]See Subsequent Hormonal Therapy (BINV-H).

[x]See Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-I).

[y]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.

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

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.

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

Continue hormonal therapy until progression or unacceptable toxicity → Progression → No clinical benefit after 3 consecutive hormonal therapy regimens or Symptomatic visceral disease

→ Yes → Chemotherapy[x] **(As in BINV-13)**

→ No → Trial of new hormone therapy[w]

No response to hormonal therapy[aa] → Chemotherapy[x] **(As in BINV-13)**

TREATMENT OF RECURRENCE

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

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

[w]See Subsequent Hormonal Therapy (BINV-H).
[x]See Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-I).
[aa] 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.

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

BINV-14

SURGICAL AXILLARY STAGING - STAGE I, IIA, AND IIB

Clinical Stage I/II → Sentinel lymph node candidate - Meeting ALL of the following criteria:
- Unicentric cancer
- Tumor clinically < 5 cm
- No prior chemotherapy or hormonal therapy

AND

Experienced sentinel node team[1]

No → Axillary dissection level I/II

Yes →

Clinically node positive at time of diagnosis[2] → FNA or core biopsy negative → Axillary dissection level I/II

Clinically node negative at time of diagnosis →

Axillary dissection level I/II

or

Sentinel node mapping and excision[3,4] →

- Sentinel node negative[5] → No further surgery
- Sentinel node positive[5] → 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 histologic 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]Sentinel node involvement defined by multilevel node sectioning with hematoxylin and eosin staining. Cytokeratin Immunohistochemistry (ICH) may be used for equivocal cases on H&E. Routine cytokeratin IHC to define node involvement is controversial (category 3).

Return to Locoregional Treatment (BINV-2)

Return to Breast Cancer Guideline Table of Contents

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

BINV-A

AXILLARY DISSECTION

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

Sentinel lymph node biopsy may be considered an option if there is an experienced sentinel node team and the patient is an appropriate sentinel lymph node biopsy candidate **(See 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.

BINV-B

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.[1] For these patients, the use of a higher radiation boost dose to the tumor bed should be considered.

Margins should be evaluated on all surgical specimens from breast conserving surgery. Requirements for optimal margin evaluation include:
- Orientation of the surgical specimens.
- Description of the gross and microscopic margin status
- Reporting of the distance, orientation, and type of tumor (invasive or DCIS) in relation to the closest margin

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

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

BINV-C

CONTRAINDICATIONS TO BREAST-CONSERVING THERAPY REQUIRING RADIATION THERAPY

Contraindications for breast-conserving therapy requiring radiation therapy include:

Absolute:
- **Prior RT to the breast or chest wall**
- **RT during pregnancy**
- **Diffuse suspicious or malignant appearing microcalcifications**
- **Multicentric disease**
- **Positive pathologic margin[1]**

Relative:
- **Multifocal disease requiring two or more separate surgical incisions.**
- **Active connective tissue disease involving the skin (especially scleroderma and lupus)**
- **Tumors > 5 cm (category 2B)**
- **Focally positive margin[1]**

**Return to Breast
Cancer Guideline
Table of Contents**

[1]See Margin Status in Infiltrating Carcinoma (BINV-C).

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

BINV-D

ADJUVANT HORMONAL THERAPY

Adjuvant hormonal therapy

Premenopausal[1] → Tamoxifen for 2-3 y ± ovarian suppression or ablation (category 1)

→ Postmenopausal[1]

→ Complete 5 y tamoxifen (category 1) → Letrozole for 5 y (category 1)[2]

→ Exemestane or anastrozole to complete 5 y adjuvant hormonal therapy (category 2B)[2,3]

→ Premenopausal[1] → Complete 5 y tamoxifen (category 1)

→ Postmenopausal[1] → Letrozole for 5 y (category 1)[2]

→ Premenopausal[1] → No further hormonal therapy

Postmenopausal[1]

→ Anastrozole for 5y (category 1)[2]

→ Tamoxifen for 2-3 y → Exemestane or anastrozole to complete 5 y adjuvant hormonal therapy (category 1)[2]

→ Tamoxifen to 4.5-6 y → Letrozole for 5 y (category 1)[2]

→ Women with contra-indication to aromatase inhibitors or who decline aromatase inhibitors, tamoxifen for 5 y (category 1)

[1]See Definition of Menopause (BINV-G).

[2]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.

[3]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-G).

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

BINV-E

ADJUVANT CHEMOTHERAPY [1,2,3,4]

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

Node positive[5]
- FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide) or FEC/CEF (cyclophosphamide/epirubicin/fluorouracil)
- AC (doxorubicin/cyclophosphamide) ± sequential paclitaxel[6]
- EC (epirubicin/cyclophosphamide)
- TAC (docetaxel/doxorubicin/cyclophosphamide) with filgrastim support[6]
- A→CMF[7] (doxorubicin followed by cyclophosphamide/methotrexate/fluorouracil)
- E→CMF (epirubicin followed by cyclophosphamide/methotrexate/fluorouracil)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC x 4 (doxorubicin/cyclophosphamide) + sequential paclitaxel x 4, every 2 weekly regimen with filgrastim support[8]
- A→T→C (doxorubicin followed by paclitaxel followed by cyclophosphamide) every 2 weekly regimen with filgrastim support[8]

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

[2]In patients with breast cancer that over-express HER-2 (IHC 3+ or FISH amplified at the level of 2.1 or greater) and with 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 that over-express HER-2. (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 cardiac monitoring, and by either the weekly or every three weekly schedule.

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

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

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

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

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

[8]A 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.

REPRESENTATIVE ADJUVANT CHEMOTHERAPY REGIMENS FOR BREAST CANCER*

COMBINATIONS

FAC chemotherapy [1,2]
- 5-Fluorouracil 500 mg/m^2 IV days 1 & 8 or days 1 & 4
- Doxorubicin 50 mg/m^2 IV day 1
  (or by 72 h continuous infusion)
- Cyclophosphamide 500 mg/m^2 IV day 1
Cycled every 21 days for 6 cycles.

CAF chemotherapy [3]
- 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 for 6 cycles.

AC chemotherapy [4]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1
Cycled every 21 days for 4 cycles.

EC chemotherapy [5]
- Epirubicin 100 mg/m^2 IV day 1
- Cyclophosphamide 830 mg/m^2 IV day 1
Cycled every 21 days for 8 cycles.

AC followed by paclitaxel chemotherapy [6,7]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1
Cycled every 21 days for 4 cycles.
Followed by
- Paclitaxel 175-225 mg/m^2 by 3 h IV infusion day 1
Cycled every 21 days for 4 cycles.

Dose-dense AC followed by paclitaxel chemotherapy [8]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1
Cycled every 14 days for 4 cycles.
Followed by
- Paclitaxel 175 mg/m^2 by 3 h IV infusion day 1
Cycled every 14 days for 4 cycles.
(All cycles are with filgrastim support).

Dose-dense A-T-C chemotherapy [8]
- Doxorubicin 60 mg/m^2 IV day 1
Cycled every 14 days for 4 cycles.
Followed by
- Paclitaxel 175 mg/m^2 by 3 h IV infusion day 1
Cycled every 14 days for 4 cycles.
Followed by
- Cyclophosphamide 600 mg/m^2 IV day 1
Cycled every 14 days for 4 cycles.
(All cycles are with filgrastim support).

*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*

CMF chemotherapy [9]
- 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 for 6 cycles.

TAC chemotherapy [10]
- Docetaxel 75 mg/m^2 IV day 1
- Doxorubicin 50 mg/m^2 IV day 1
- Cyclophosphamide 500 mg/m^2 IV day 1
Cycled every 21 days for 6 cycles.
(All cycles are with filgrastim support).

A followed by CMF [11]
- Doxorubicin 75 mg/m^2 IV day 1
Cycled every 21 days for 4 cycles.
Followed by
- Cyclophosphamide 600 mg/m^2 IV day 1
- Methotrexate 40 mg/m^2 IV day 1
- 5-Fluorouracil 600 mg/m^2 IV day 1
Cycled every 21 days for 8 cycles.

E followed by CMF [12]
- Epirubicin 100 mg/m^2 IV day 1
Cycled every 21 days for 4 cycles.
Followed by
- 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 for 4 cycles.
OR
- Cyclophosphamide 750 mg/m^2 IV day 1
- Methotrexate 50 mg/m^2 IV day 1
- 5-Fluorouracil 600 mg/m^2 IV day 1
Cycled every 21 days for 4 cycles.

FEC chemotherapy [13]
- Cyclophosphamide 75 mg/m^2 PO days 1-14
- Epirubicin 60 mg/m^2 IV days 1 & 8
- 5-Fluorouracil 500 mg/m^2 IV days 1 & 8
With cotrimoxazole support.
Cycled every 28 days for 6 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.

REFERENCES FOR REPRESENTATIVE ADJUVANT CHEMOTHERAPY REGIMENS FOR BREAST CANCER

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

[2]Assikis V, Buzdar A, Yang Y, et al: A phase III trial of sequential adjuvant chemotherapy for operable breast carcinoma: final analysis with 10-year follow-up. Cancer 97:2716-23, 2003

[3]Bull JM, Tormey DC, Li SH, et al: A randomized comparative trial of adriamycin versus methotrexate in combination drug therapy. Cancer 41:1649-57, 1978

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

[5]Piccart MJ, Di Leo A, Beauduin M, et al: Phase III Trial Comparing Two Dose Levels of Epirubicin Combined With Cyclophosphamide With Cyclophosphamide, Methotrexate, and Fluorouracil in Node-Positive Breast Cancer. J Clin Oncol 19:3103-3110, 2001

[6]Henderson IC, Berry DA, Demetri GD, et al: Improved Outcomes From Adding Sequential Paclitaxel but Not From Escalating Doxorubicin Dose in an Adjuvant Chemotherapy Regimen for Patients With Node-Positive Primary Breast Cancer. J Clin Oncol 21:976-983, 2003

[7]Mamounas EP, Bryant J, Lembersky BC, et al: Paclitaxel (T) following doxorubicin/cyclophosphamide (AC) as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28. Proc Am Soc Clin Oncol 22:Abstract 12, 2003

[8]Citron ML, Berry DA, Cirrincione C, et al: Randomized Trial of Dose-Dense Versus Conventionally Scheduled and Sequential Versus Concurrent Combination Chemotherapy as Postoperative Adjuvant Treatment of Node-Positive Primary Breast Cancer: First Report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 21:1431-1439, 2003

[9]Goldhirsch A, Colleoni M, Coates AS, et al: Adding adjuvant CMF chemotherapy to either radiotherapy or tamoxifen: are all CMFs alike? The International Breast Cancer Study Group (IBCSG). Ann Oncol 9:489-93, 1998

[10]Nabholtz J-M, Pienkowski T, Mackey J, et al: Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node positive breast cancer (BC) patients: interim analysis of the BCIRG 001 study. Proc Am Soc Clin Oncol 21:Abstract 141, 2002

[11]Bonadonna G, Zambetti M, Valagussa P: Sequential or alternating doxorubicin and CMF regimens in breast cancer with more than three positive nodes. Ten-year results. JAMA 273:542-7, 1995

[12]Poole CJ, Earl HM, Dunn JA, et al: NEAT (National Epirubicin Adjuvant Trial) and SCTBG BR9601 (Scottish Cancer Trials Breast Group) phase III adjuvant breast trials show a significant relapse-free and overall survival advantage for sequential ECMF. Proc Am Soc Clin Oncol 22:Abstract 13, 2003

[13]Levine MN, Bramwell VH, Pritchard KI, et al: Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 16:2651-8, 1998

*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.

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 $\geq$ 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 time of adjuvant chemotherapy, amenorrhea is not a reliable indicator of menopausal status.

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

BINV-G

SUBSEQUENT HORMONAL THERAPY FOR SYSTEMIC DISEASE
(For first-line hormonal therapy see BINV-13)

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

POSTMENOPAUSAL PATIENTS
- **Non-steroidal aromatase inhibitor (anastrozole, letrozole)
  or steroidal aromatase inactivator (exemestane)**
- **Fulvestrant**
- **Tamoxifen or Toremifene**
- **Megestrol acetate**
- **Fluoxymesterone**
- **Ethinyl estradiol**

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

BINV-H

PREFERRED CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER[1] (page 1 of 6)

Preferred Single Agents

- Doxorubicin
- Epirubicin
- Pegylated liposomal doxorubicin
- Paclitaxel
- Docetaxel
- Capecitabine
- Vinorelbine
- Gemcitabine (category 2B)

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)

Other Active Agents

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

PREFERRED CHEMOTHERAPY REGIMENS FOR USE IN COMBINATION WITH TRASTUZUMAB
(HER-2 over-expressed metastatic disease)

Paclitaxel ± Carboplatin
Docetaxel ± Carboplatin
Vinorelbine

[1]There is no compelling evidence that combination regimens are superior to sequential single agents.

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 1250 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.

REPRESENTATIVE CHEMOTHERAPY REGIMENS FOR METASTATIC BREAST CANCER* (Page 3 of 6)

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 (category 2B) 800-1200 mg/m^2 IV days 1, 8 & 15
  Cycled every 28 days. [17]**

*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 CHEMOTHERAPY REGIMENS FOR METASTATIC BREAST CANCER IN COMBINATION WITH TRASTUZUMAB* (Page 4 of 6)

CHEMOTHERAPY COMPONENT

COMBINATIONS

PCH [18]
- **Carboplatin AUC of 6 IV day 1**
- **Paclitaxel 175 mg/m^2 by 3 h IV infusion day 1**
Cycled every 21 days.

SINGLE AGENTS

- **Paclitaxel 175 mg/m^2 by 3 h IV infusion day 1**
  Cycled every 21 days. [19]
  OR
- **Paclitaxel 80-90 mg/m^2 by 1 h IV infusion weekly** [20]

- **Docetaxel 80 to 100 mg/m^2 by 30 min IV infusion day 1**
  Cycled every 21 days
  OR
- **Docetaxel 35 mg/m^2 by 30 min IV infusion weekly** [21]

- **Vinorelbine 25 mg/m^2 IV weekly** [15,22]

TRASTUZUMAB COMPONENT

Trastuzumab 4 mg/kg IV by 90 min infusion day 1
Followed by
2 mg/kg IV by 30 min infusion weekly [19,23]
OR
Trastuzumab 8 mg/kg IV by 90 min infusion day 1
Followed by
6 mg/kg IV by 90 min infusion every 3 weeks [24]

*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.

REFERENCES FOR REPRESENTATIVE CHEMOTHERAPY REGIMENS FOR METASTATIC BREAST CANCER and in COMBINATION WITH TRASTUZUMAB* (Page 5 of 6)

[1]Bull JM, Tormey DC, Li SH, et al: A randomized comparative trial of adriamycin versus methotrexate in combination drug therapy. Cancer 41:1649-57, 1978

[2]Hortobagyi GN, Gutterman JU, Blumenschein GR, et al: Combination chemoimmunotherapy of metastatic breast cancer with 5-fluorouracil, adriamycin, cyclophosphamide, and BCG. Cancer 43:1225-33, 1979

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

[4]Bonadonna G, Brusamolino E, Valagussa P, et al: Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 294:405-10, 1976

[5]O'Shaughnessy J, Miles D, Vukelja S, et al: Superior Survival With Capecitabine Plus Docetaxel Combination Therapy in Anthracycline-Pretreated Patients With Advanced Breast Cancer: Phase III Trial Results. J Clin Oncol 20:2812-2823, 2002

[6]Albain K.S., Nag S., et al: Global Phase lll Study of Gemcitabine Plus Paclitaxel (GT) vs. Paclitaxel (T) as Frontline Therapy for Metastatic Breast Cancer (MBC); First Report of Overall Survival. J Clin Oncol 22 No 14S: 510, 2004.

[7]Ackland SP, Anton A, Breitbach GP, et al: Dose-Intensive Epirubicin-Based Chemotherapy Is Superior to an Intensive Intravenous Cyclophosphamide, Methotrexate, and Fluorouracil Regimen in Metastatic Breast Cancer: A Randomized Multinational Study. J Clin Oncol 19:943-953, 2001

[8]Gundersen S, Kvinnsland S, Klepp O, et al: Weekly adriamycin versus VAC in advanced breast cancer. A randomized trial. Eur J Cancer Clin Oncol. 22:1431-4, 1986

[9]Bastholt, L., Dalmark, M., et al: Dose-Response Relationship of Epirubicin in the Treatment of Postmenopausal Patients with Metastatic Breast Cancer: A Randomized Study of Epirubicin at Four Different Dose Levels Performed by the Danish Breast Cancer Coopertive Group.J Clin Oncol 14: 1146-1155, 1996.

[10]O'Brien, M. E., Wigler, N., et al: Reduced Cardiotoxicity and Comparable Efficacy in a Phase lll Trial of Pegylated Liposomal Doxorubicin HC1 (CAELYX/Doxil) vs. Conventional Doxorubicin for First-Line Treatment of Metastatic Breast Cancer. Ann Oncol 15(3): 440-9, 2004

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

[12]Perez EA, Vogel CL, Irwin DH, et al: Multicenter Phase II Trial of Weekly Paclitaxel in Women With Metastatic Breast Cancer. J Clin Oncol 19:4216-4223, 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.

REFERENCES FOR REPRESENTATIVE CHEMOTHERAPY REGIMENS FOR METASTATIC BREAST CANCER and in COMBINATION WITH TRASTUZUMAB* (Page 6 of 6)

[13] Burris HAR: Single-agent docetaxel (Taxotere) in randomized phase III trials. Semin Oncol. 26:1-6, 1999

[14] Valero V: Docetaxel as single-agent therapy in metastatic breast cancer: clinical efficacy. Semin Oncol. 24(Suppl 13):S11-18, 1997

[15] Burstein HJ, Manola J, Younger J, et al: Docetaxel Administered on a Weekly Basis for Metastatic Breast Cancer. J Clin Oncol 18:1212-1219, 2000

[16] Zelekv L, Barthier S, Riofrio M, et al: Weekly vinorelbine is an effective palliative regimen after failure with anthracyclines and taxanes in metastatic breast carcinoma. Cancer 92:2267-72, 2001

[17] Seidman AD: Gemcitabine as single-agent therapy in the management of advanced breast cancer. Oncology (Huntingt) 15(Suppl 3):11-14, 2001

[18] Robert N, Leyland-Jones B, Asmar L, et al: Phase III comparative study of trastuzumab and paclitaxel with and without carboplatin in patients with HER-2/neu positive advanced breast cancer. 25th Annual San Antonio Breast Cancer Symposium:Abstract 35, 2002

[19] Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344:783-92, 2001

[20] Seidman AD, Fornier MN, Esteva FJ, et al: Weekly Trastuzumab and Paclitaxel Therapy for Metastatic Breast Cancer With Analysis of Efficacy by HER2 Immunophenotype and Gene Amplification. J Clin Oncol 19:2587-2595, 2001

[21] Esteva FJ, Valero V, Booser D, et al: Phase II Study of Weekly Docetaxel and Trastuzumab for Patients With HER-2-Overexpressing Metastatic Breast Cancer. J Clin Oncol 20:1800-1808, 2002

[22] Burstein HJ, Kuter I, Campos SM, et al: Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer. J Clin Oncol 19:2722-30, 2001

[23] Cobleigh MA, Vogel CL, Tripathy D, et al: Multinational Study of the Efficacy and Safety of Humanized Anti-HER2 Monoclonal Antibody in Women Who Have HER2-Overexpressing Metastatic Breast Cancer That Has Progressed After Chemotherapy for Metastatic Disease. J Clin Oncol 17:2639-48, 1999

[24] Leyland-Jones, Gelman et al: Pharmacokinetics, Safety, and Efficacy of Trastuzumab Administered Every Three Weeks in Combination with Paclitaxel. J Clin Oncol 21: 3965-3971, 2003.

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.

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget's)	Paget's disease of the nipple with no tumor

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

T1		Tumor 2 cm or less in greatest dimension
	T1mic	Microinvasion 0.1 cm or less in greatest dimension
	T1a	Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
	T1b	Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
	T1c	Tumor more than 1 cm but not more than 2 cm in greatest dimension
T2		Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3		Tumor more than 5 cm in greatest dimension
T4		Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below
	T4a	Extension to chest wall, 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

NX		Regional lymph nodes cannot be assessed (e.g., previously removed)
N0		No regional lymph node metastasis
N1		Metastasis to movable ipsilateral axillary lymph node(s)
N2		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
	N2a	Metastases in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
	N2b	Metastasis only in *clinically apparent** ipsilateral internal mammary nodes and in the *absence* of clinically evident axillary lymph node metastasis
N3		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
	N3a	Metastasis in ipsilateral infraclavicular lymph node(s)
	N3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
	N3c	Metastasis in ipsilateral supraclavicular lymph node(s)

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

ST-1

Table 1 (continued)

Pathologic (pN)[a]

pNX   Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)

pN0   No regional lymph node metastasis histologically, no additional examination for isolated tumor cells (ITC)

Note: Isolated tumor cells (ITC) are defined as single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by immonohistochemical (IHC) or molecular methods but which may be verified on H&E stains. ITCs do not usually show evidence of malignant activity e.g., proliferation or stromal reaction.

    pN0(i-)   No regional lymph node metastasis histologically, negative IHC

    pN0(i+)   No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm

    pN0(mol-)   No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)[b]

    pN0(mol+)   No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)[b]

[a]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***

    pN1c   Metastasis in 1 to 3 axillary lymph nodes and in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not *clinically apparent*.** (If associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden)

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.

NCCN®

Practice Guidelines in Oncology – v.2.2005

Breast Cancer

Guidelines Index
Breast Cancer TOC
Staging, MS, References

Table 1 (continued)

Distant Metastasis (M)

MX   Distant metastasis cannot be assessed

M0   No distant metastasis

M1   Distant metastasis

STAGE GROUPING

Stage	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1*	N0	M0
Stage IIA	T0	N1	M0
	T1*	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0

Stage	T	N	M
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

* T1 includes T1mic

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

The histopathologic types are the following:

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.[1,2] 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.

[1] Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histologic grade in breast cancer: experience from a large study with long-term follow-up. Histopathololology 1991;19:403-410.

[2.] Fitzgibbons PL, Page DL, Weaver D et al. Prognostic factors in breast cancer. College of American Pathologists consensus statement 1999. Arch Pathol Lab Med 2000;124:966-978.

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)

Manuscript

NCCN Categories of Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Overview

The American Cancer Society estimates that approximately 217,440 new cases of breast cancer will be diagnosed in the United States in the year 2004, and approximately 40,580 patients will die of this disease.[1] 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. This suggests a benefit from early detection and more effective treatment.[1]

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 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 mutations in the genes *BRCA1* and *BRCA2*. However, except for female gender and increasing age, these risk factors are associated with only a minority of breast cancers. Women with a strong family history of breast cancer should be evaluated according to the NCCN Genetics/Family Screening Guideline. Women at increased risk for breast cancer (generally those with a greater than 1.67% 5-year risk of breast cancer) may consider risk reduction strategies (see NCCN Breast Cancer Risk Reduction Guideline).

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

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).[2,3] 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) 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 histologic evidence of malignant activity. All metastatic lesions to ipsilateral axillary lymph nodes no larger than 0.2 mm, whether detected by H&E 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.[4]

2) Identifiers are added to indicate the use of sentinel lymph node dissection and immunohistochemical or molecular pathology techniques.

3) The number of involved nodes as determined by routine hematoxylin and eosin staining (preferred method) or by immunohistochemistry 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 IIIC 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 pathologic techniques.[3]

Pathology Assessment

A central component of the treatment of breast cancer is full knowledge of extent and microscopic 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 HER2). These factors are determined by examination of excised tissue and provided in a written pathology report. Accurate pathology reporting requires communication between the surgeon and the pathologist, and use of consistent, unambiguous standards for reporting. Data from both national and local surveys show that as many as 50% of pathology reports for breast cancer are missing some elements critical to patient management.[5,6] Significant omissions include failure to orient and report surgical margins and consistent reporting of tumor grade.

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 College of American Pathologists 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 Protocols of the College of American Pathologists for reporting the pathological analysis of all breast specimens.

Treatment Approach

Conceptually, the treatment of breast cancer (except lobular carcinoma in situ [LCIS]) includes the treatment of local disease with surgery, radiation therapy (RT), or both, and the treatment of systemic disease with cytotoxic chemotherapy or hormonal therapy. 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, level of HER2/neu expression, presence or absence of detectable metastatic disease, comorbidity, and the patient's age and menopausal status. Breast cancer does occur in men, and men with breast cancer should be treated similarly to postmenopausal women. Patient preference is also 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, locoregional invasive carcinoma (clinical stage I, stage II, and some stage IIIA tumors); 3) inoperable locoregional invasive carcinoma (clinical stage IIIB, stage IIIC, and some stage IIIA tumors); and 4) metastatic or recurrent carcinoma (stage IV).

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

Pure Noninvasive Carcinomas (Stage 0)

Both LCIS and DCIS may be difficult to distinguish from atypical hyperplasia or from carcinomas with early invasion.[7,8] 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 in situ carcinomas is either preventing the occurrence of invasive disease or diagnosing the invasive component when still localized to the breast. Patients found to have invasive disease on pathology review or at the time of re-excision or mastectomy 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).[9] The histologies of the invasive carcinomas tend to be favorable, and deaths from second invasive cancers are unusual in appropriately monitored women.[10] Bilateral mastectomy, with or without reconstruction, can be considered in special circumstances.

The risk of an invasive breast cancer after a diagnosis of LCIS is equal in both breasts. 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.

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 in the risk of developing invasive breast cancer among women with a history of LCIS.[11] Therefore, the use of tamoxifen should be considered as a risk reduction strategy in women with LCIS who are treated with observation. (For recommendations on risk reduction, see the NCCN Breast Cancer Risk Reduction Guideline.)

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. Women treated with mastectomy are appropriate candidates for breast reconstruction. Contraindications to breast-conserving therapy with radiation therapy are listed in the algorithm (BINV-D).

Prospective randomized trials have shown that the addition of breast irradiation to a margin-free excision of pure DCIS decreases the rate of in-breast disease recurrence, but does not affect overall survival.[12,13] Although some non-controlled evidence suggests that selected patients have a low risk of local failure with excision alone without breast irradiation,[14,15] based on high-level evidence from randomized trials, the NCCN Guideline calls for the use of radiation after excision alone in all patients with DCIS 0.5 cm or greater in diameter. The use of radiation after breast-conserving surgery reduces the relative risk of a local failure by approximately a half. The use of a radiation boost (by photons, brachytherapy, or electron beam) to the tumor bed is recommended to maximize local control, especially in patients 50 years of age or younger. Many factors, including patient age, tumor size and grade, and minimal width of the margins, impact this recurrence risk. The definition of a negative margin has not been firmly established in this disease. There appears to be a consensus that margins greater than 10 mm are negative and margins less than 1 mm are inadequate, but no uniform consensus exists for margin status between these values.

Finally, because the choice of local treatment does not impact a patient's disease related survival, the patient's acceptance for potential increased risk of local failure 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. 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, and without lymph node dissection,

3) Excision alone followed by observation.

A number of prospective studies are underway evaluating the pathologic classification systems and treatment options for DCIS. The results of these studies may require modifications to the current guidelines.

Patients with mammographically detected DCIS who elect breast conservation therapy should undergo postexcision 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 microcalcifications) is clearly within the specimen (category 3). This recommendation is considered category 3 because of disagreement on whether specimen radiographs interpreted as showing removal of all microcalcifications and masses are adequate documentation of complete excision. Clips are used by some NCCN institutions to demarcate the biopsy area because DCIS is usually 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.[11] These data also showed that tamoxifen led to a substantial reduction in the risk of developing benign breast disease.[16] The Early Breast Cancer Trialists' overview analysis showed that, with 5 years of tamoxifen therapy, women with estrogen receptor (ER) -positive or receptor-unknown tumors had a 47% reduction in the annual odds of recurrence of invasive breast cancer.[17] Similarly, the NSABP B-24 trial found a benefit from tamoxifen in women with DCIS after treatment with breast conservation surgery (BCS) and RT. In this 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.[18] 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.[19]

Tamoxifen treatment, therefore, may be considered in 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 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 radiography, bilateral diagnostic mammography, and, if necessary, breast ultrasonography, tumor estrogen and progesterone receptor determinations, level of HER2/*neu* expression, and pathology review. Evaluation of the breast with magnetic resonance imaging (MRI) using a dedicated breast coil in women considering breast-conserving therapy is optional, if available. However, 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 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 level of HER2/*neu* expression for all newly diagnosed invasive breast cancers is recommended. HER2/*neu* level of expression may be used to provide prognostic information, to predict for the superiority of anthracycline-based adjuvant chemotherapy over cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy, and to predict for benefit from trastuzumab therapy in women with recurrent or metastatic breast cancer. Only the use of HER2/*neu* expression to predict for trastuzumab sensitivity has been prospectively studied. HER2/*neu* expression has been assessed by measuring the number of gene copies (fluorescence in situ hybridization [FISH]), the number of cell surface receptors (immunohistochemistry [IHC]), or by level of circulating receptor protein. Several different methodologies have been used to perform these determinations, but only a few have United States Food and Drug Administration approval. These methodologies include: 1) the IHC HercepTest (DAKO, Glostrup, Denmark) and the IHC PATHWAY Her 2 (Ventana Medical Systems, Tucson, AZ), which are approved for predicting responsiveness to trastuzumab; 2) the INFORM HER-2/*neu* FISH test (Ventana Medical Systems) for assigning prognosis; and 3) the PathVysion HER-2 DNA Probe Kit FISH test (Vysis, Downers Grove, IL) for prognosis, for predicting anthracycline sensitivity, and for re-predicting responsiveness to trastuzumab. Adequate standardization of HER2 assays used in clinical practice outside high-volume central facilities is a concern, and limited study suggests that false-positive determinations are common in low-volume testing facilities.[20,21] Although determination of HER2/*neu*

gene amplification by FISH is substantially more costly than determination of HER2/*neu* expression by IHC, FISH determinations may also be more accurate.[22,23]

Determining HER2/*neu* expression in the initial work-up is recommended for prognostic purposes in patients with node-negative breast cancer (category 2B).[24] It also assists in the selection of adjuvant therapy. Retrospective data suggest that doxorubicin-based adjuvant therapy may be superior to non-doxorubicin-based chemotherapy in patients with tumors which overexpress HER2/*neu* (category 2B),[25-28] and provides baseline information to be considered should the individual develop recurrent disease requiring consideration of trastuzumab therapy (category 1).[29-31] The relative role of IHC versus FISH testing for HER2/neu expression or amplification in providing prognostic or predictive information has not yet been fully defined.[32-35] However, early data suggest that amplified HER2/*neu* by FISH analysis is a better predictor of trastuzumab responsiveness than IHC for patients with HER2/*neu* expression of 2+ by the HercepTest.

Locoregional treatment

A number of randomized trials document that, in the majority of women with stage I and stage II breast cancers, mastectomy with axillary lymph node dissection or breast-conserving therapy with lumpectomy, axillary dissection, and breast irradiation (breast-conserving therapy) are medically equivalent primary treatment options (category 1).[36-39]

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, have diffuse suspicious or malignant-appearing microcalcifications on mammography, have multicentric disease (ie, disease involving 2 or more quadrants of the breast), or have a positive pathologic margin. Patients with a pathologically positive margin may undergo re-excision(s) to achieve a negative pathologic margin. If the pathologic margins remain positive after re-excisions, then mastectomy is required for optimal local disease control. In order to adequately assess pathologic margins following lumpectomy, the Panel recommends that the surgical specimens be oriented, that the pathologist provide a description of the gross and microscopic margin status, and the distance, orientation, and type of tumor (invasive or DCIS) in relation to the closest margin be described.

Relative contraindications to breast-conserving therapy include multifocal disease requiring 2 or more separate surgical excisions, active connective tissue disease involving the skin (especially scleroderma and lupus), tumors greater than 5 cm (category 2B), and focally positive pathologic margins. 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.

Recent results from an Intergroup CALGB/RTOG/ECOG study have focused on women with early stage breast cancer who are 70 years of age or older at diagnosis. These women had Stage I, estrogen receptor positive breast cancer, and were randomized to receive whole breast radiation plus tamoxifen for 5 years, or tamoxifen alone. Locoregional recurrence rates were 1% in the radiation arm, and 4% in the tamoxifen arm. No differences were found in survival, disease free survival or need for mastectomy. The current version of the guideline allows 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 node, ER positive breast cancer

(category 1 with tamoxifen; category 2B with an aromatase inhibitor).[40] Similar results were also obtained in another study of similar design.[41]

If adjuvant chemotherapy is indicated, RT should be given after chemotherapy is completed.[42] 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.[43-45] The Guideline recommends regional lymph node RT in patients treated with breast-conserving surgery analogous to that recommended in patients treated with postmastectomy regional lymph node irradiation (see subsequent discussion).

The NCCN Breast Cancer Treatment Guidelines include a guideline for surgical axillary staging for stages I, IIA, and IIB breast cancer (BINV-A). A typical woman with clinical stage I or stage II breast cancer requires pathologic assessment of the axillary lymph node status. Traditionally, pathologic assessment of axillary lymph nodes has required the performance of a formal level I and level II axillary dissection. At least 10 lymph nodes should be provided for pathologic evaluation to accurately stage the axilla with the level I and level II dissection.[46,47] The axillary dissection should be extended to include level III nodes only if gross disease is apparent in the level I or II nodes.

The surgical axillary staging guideline allows for the performance of a sentinel lymph node biopsy in certain circumstances to assess the pathologic status of the axillary lymph nodes.[48-54] Not all women are

candidates for sentinel lymph node biopsy. Appropriate candidates are those for whom an experienced sentinel lymph node team is available.[55] In addition, potential candidates should have clinically negative axillary lymph nodes, or a negative core or fine needle aspiration (FNA) biopsy of any clinically suspicious axillary lymph node and a primary tumor less than 5 cm in greatest diameter. If the sentinel lymph node cannot be identified or is positive for metastasis, a formal axillary lymph node dissection should be performed. If lymph node mapping identifies sentinel lymph nodes in the internal mammary chain, internal mammary node excision is considered optional (category 3). In many institutions, sentinel lymph nodes are assessed for the presence of metastasis by both hematoxylin and eosin staining and cytokeratin IHC. The clinical significance of a lymph node that is negative by hematoxylin and eosin 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 hematoxylin and eosin staining, the panel believes that current treatment decisions should be made based solely on hematoxylin and eosin staining (category 3). In the uncommon situation in which hematoxylin and eosin staining is equivocal, reliance on the results of cytokeratin IHC is reasonable.

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

Furthermore, in the absence of definitive data demonstrating superior survival with axillary lymph node dissection or sentinel lymph node biopsy, 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, elderly patients, and patients with serious comorbid conditions. Women who do not undergo axillary dissection or axillary lymph node irradiation are at increased risk for ipsilateral lymph node recurrence.[56] 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 size. 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. The current Guideline allows the performance of pretreatment sentinel lymph node biopsy in those women with clinically negative axillary examinations. 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 local, 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.[57] 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 docetaxel for 4 cycles followed by local therapy, or local therapy followed by 4 cycles of postoperative docetaxel. Early results from 2500 women in NSABP B-27 show a higher rate of complete pathologic response at surgery in patients treated with 4 cycles of AC followed by 4 cycles of docetaxel versus 4 cycles of AC alone. Disease-free survival and overall survival have not yet been reported for B-27, and no difference in clinical outcome between preoperative versus postoperative docetaxel has been reported.

A number of chemotherapy regimens have been studied as preoperative chemotherapy in this setting. The panel believes that the regimens recommended in the adjuvant setting (see BINV-F) are appropriate to consider in the preoperative chemotherapy setting.

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 between tamoxifen, anastrozole, anastrozole plus tamoxifen, or letrozole. These studies consistently demonstrate that the use of either anastrozole or letrozole alone provide superior rates of breast conserving surgery and usually objective response.[58-60] On the basis of these trials, the panel has

added preoperative hormonal therapy with an aromatase inhibitor as an option on the Preoperative Treatment Guideline (see BINV-8) in the treatment of postmenopausal women with hormone receptor positive disease.

If the tumor responds to preoperative chemotherapy, lumpectomy plus axillary lymph node dissection may be considered if the requirements for breast-conserving therapy are fulfilled. BCS 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, tamoxifen in women with estrogen receptor-positive tumors, and RT to the chest wall and supraclavicular 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
Patients treated with total mastectomy whose tumors are more than 5 cm in greatest diameter or who have positive surgical margins are at sufficiently high risk for local recurrence to warrant the use of postmastectomy radiotherapy to the chest wall (category 2A), as well as consideration of radiotherapy to the supraclavicular (category 2B) and internal mammary (category 3) lymph nodes.

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.[61-65] In these trials, not only the ipsilateral chest wall but also the ipsilateral locoregional lymph nodes were irradiated. These studies contrast, however, with a number of other studies, including a randomized trial from an NCCN institution.[66] These other studies fail 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 such women.

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, with consideration also given to the inclusion of the ipsilateral internal mammary field (category 3). The recommendation for chest wall and supraclavicular irradiation 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 other studies that do not show an advantage. This is an unusual situation in which high-level evidence (category 1) exists but is contradictory.

Furthermore, there was considerable disagreement regarding the inclusion of the ipsilateral internal mammary field. Some panel

NCCN®

Practice Guidelines in Oncology – v.2.2005

Breast Cancer

Guidelines Index
Breast Cancer TOC
Staging, MS, References

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. 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.[37] Again, there was substantial disagreement among panel members regarding the inclusion of the ipsilateral internal mammary field (category 3).

Other features in node-negative tumors that predict a high rate of local recurrence include primary tumors greater than 5 cm, positive pathologic margins, and close (< 1 mm) pathologic margins. Chest wall RT is recommended in patients with negative axillary lymph nodes and with tumors greater than 5 cm or with positive pathologic margins. 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 (< 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 local 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.[17,67] Thus, for those under age 70, the current guidelines recommend adjuvant therapy without regard to patient age. 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, the toxicity of the therapy, and comorbidity.[68,69] The decision-making process requires a collaboration involving the health care provider and the patient.

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.[17] Selected studies suggest that breast cancers that overexpress the HER2/*neu* oncogene may be relatively hormone refractory, although other studies have failed to confirm this finding.[27,70-74] 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 women with hormone receptor-positive breast cancer regardless of menopausal status, age, or HER2/*neu* status, with the exception of 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.

The most firmly established adjuvant endocrine therapy is tamoxifen for both premenopausal and postmenopausal women.[17] In women with hormone estrogen receptor positive or unknown breast cancer, adjuvant tamoxifen decreases the annual odds of recurrence by

47% and the annual odds of death by 26%. Benefit to tamoxifen in women with hormone receptor positive or unknown breast cancer is observed regardless of age, menopausal status, lymph node status, or whether or not chemotherapy is used.[17] Several studies have recently been reported utilizing aromatase inhibitors in the treatment of postmenopausal women with early breast cancer. These studies have utilized the aromatase inhibitors either as initial adjuvant therapy, sequentially 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.

The Arimidex, Tamoxifen, Alone or in Combination Trial (ATAC Trial) demonstrates 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.[75] With a median of 47 months follow-up, results in 9366 postmenopausal women with early breast cancer enrolled in the ATAC Trial demonstrate fewer recurrences (hazard ratio 0.83; 95% CI 0.76 - 0.96; P = 0.015) with anastrozole compared with tamoxifen. In the subset of women with hormone receptor-positive breast cancer the benefit was greater (hazard ratio 0.78; 95% CI 0.65 - 0.93; P =0.007).[76] 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.[77] 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 complete elimination of endogenous estrogen levels. No survival results are yet available from the ATAC Trial. ATAC Trial subprotocols show a lesser effect of

anastrozole compared with tamoxifen on endometrial tissue,[78] no deleterious effect on quality of life,[79] and a small pharmacokinetic interference of unclear significance.[80] Further follow-up will allow for better characterization of the impact on survival and the toxicity profile of anastrozole in the adjuvant setting.

Two trials that studied the sequential use of tamoxifen followed by a third generation aromatase inhibitors versus continued tamoxifen have been reported. The 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.[81] The hazard rate for relapse strongly favored sequential treatment with anastrozole (Hazard ratio 0.36; 95% CI 0.17 - 0.75; P=0.006) with a trend towards fewer deaths (Hazard ratio 0.18; 95% CI 0.02 - 1.57; P=0.07). The 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.[82] The results at a median of 30.6 months of follow-up demonstrated the superiority of sequential exemestane in disease free survival (hazard ratio 0.64; 95% CI 0.56 - 0.82; P<0.001) with no difference in overall survival (hazard ratio 0.88; 95% CI 0.67 - 1.16; 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).

Results of the MA17 trial in 5187 women who had completed 4.5-6 years of adjuvant tamoxifen demonstrates that extended therapy with letrozole provides benefit in women with hormone receptor

positive, early breast cancer patients who are postmenopausal at the completion of the tamoxifen therapy.[83] With a median follow-up of 2.4 years, the results demonstrate fewer recurrences or new contralateral breast cancers with extended letrozole (hazard ratio 0.57; 95% CI 0.43 - 0.75; P=0.00008). No difference in overall survival was demonstrated.

The differences in design and patient population between the studies of the aromatase inhibitors do not allow for the direct comparison of the results of these studies. The studies are consistent in demonstrating that the use of a third generation aromatase inhibitor in postmenopausal women with hormone receptor positive breast cancer is superior to tamoxifen alone when used as either initial adjuvant therapy, sequential therapy, or extending therapy. Thus, the current version of the guideline has been modified relating to the endocrine therapy of postmenopausal women with early breast cancer to allow for the use of an aromatase inhibitor as either initial adjuvant therapy, sequential with tamoxifen, or as extended therapy in those situations where endocrine therapy is to be utilized. The guideline recommends the specific aromatase inhibitor(s) that have been demonstrated to be superior to tamoxifen alone in the specific clinical setting. 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. It should be 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.

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.[84] 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 angiolymphatic invasion, high nuclear grade, high histologic grade, HER-2 overexpression, 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.

The guidelines also provide systemic treatment recommendations for the favorable-histology invasive breast cancers, such as tubular and colloid cancers, based on tumor size. 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 Breast Cancer Guideline Panel believes that including medullary carcinoma with other special histology cancers that 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.

Patients with lymph node involvement or with tumors greater than 1 cm in diameter are appropriate candidates for adjuvant systemic therapy (category 1). For women with lymph node-negative, hormone receptor-negative tumors greater than 1 cm in diameter, chemotherapy is recommended (category 1). For those with lymph node-negative, hormone receptor-positive tumors greater than 1 cm but not more than 3 cm in diameter, endocrine therapy with chemotherapy is recommended (category 1). The use of 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.

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.[85] 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.

For axillary lymph node-negative breast cancer, appropriate chemotherapy regimens include cyclophosphamide, methotrexate, and 5-fluorouracil (CMF); fluorouracil, doxorubicin, and cyclophosphamide (FAC/CAF); or doxorubicin and cyclophosphamide (AC). In women with node-positive disease, FAC/CAF or cyclophosphamide, epirubicin, and fluorouracil (CEF); AC alone; epirubicin and cyclophosphamide (EC); docetaxel, doxorubicin, and cyclophosphamide (TAC); AC followed by paclitaxel; doxorubicin followed by CMF, and CMF alone are all considered to be appropriate options.

Studies of CMF chemotherapy versus no chemotherapy have shown disease-free and overall survival advantages with CMF chemotherapy.[67] Studies using CAF/FAC (cyclophosphamide, doxorubicin, 5-fluorouracil) chemotherapy have shown that the use of full-dose chemotherapy regimens is important.[86] 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.[67] Based on these data, the panel qualified the appropriate chemotherapy regimens by the statement that anthracycline-containing regimens are preferred for node-positive patients. This analysis, however, did not consider the potential interaction between HER2/*neu* expression level and efficacy of anthracycline-containing versus CMF chemotherapy regimens. Retrospective analysis has suggested that the superiority of anthracycline-containing chemotherapy may be limited to the treatment of those breast cancers that overexpress the HER2/*neu* oncogene.[26,28,73,87,88] This retrospective finding across several clinical trials that doxorubicin-based chemotherapy may be more efficacious in patients whose tumors overexpress HER2/*neu*,[25,26,28,89] has led to a footnote stating that doxorubicin-based chemotherapy may be superior to non-doxorubicin-containing regimens in the adjuvant treatment of such patients (category 2B).

Doxorubicin and cyclophosphamide chemotherapy for 4 cycles has been studied in randomized trials, resulting in relapse-free and overall survival equivalent to CMF chemotherapy.[90-92] No benefit from dose escalation of either doxorubicin or cyclophosphamide was shown.[93,94] 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.[95,96]

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 one of them an improvement in overall survival with the addition of paclitaxel.[94,97] 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.[98]

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 five-year relapse-free survival (63% vs 53%; P = 0.009) and overall survival (77% vs 70%; P =0.03) favored the CEF arm of the trial.[99] The second trial compared CEF given all intravenously every 3 weeks at 2 dose levels of epirubicin (50 mg/m^2 vs 100 mg/m^2) in premenopausal and postmenopausal women with node-positive breast cancer. Five-year disease-free survival (55% vs 66%; P =0.03) and overall survival (65% vs 76%; P =0.007) both favored the epirubicin 100 mg/m^2 arm.[100] A recent trial compared 2 dose levels of EC chemotherapy with CMF chemotherapy in women with node-positive breast cancer.[101] This study showed that higher dose EC chemotherapy was equivalent to CMF chemotherapy and superior to moderate dose EC in event-free survival and overall survival.

Early results from a single randomized trial compared docetaxel, doxorubicin, and cyclophosphamide (TAC) versus FAC chemotherapy in axillary lymph node-positive breast cancer suggest

NCCN®
Practice Guidelines in Oncology – v.2.2005

Breast Cancer

Guidelines Index
Breast Cancer TOC
Staging, MS, References

that TAC is superior to FAC.[102] The advantage with TAC was observed only in those women with 1 to 3 positive axillary lymph nodes. But the difference was statistically significant in this subset, with 33 months of median follow-up for both disease-free and overall survival. Further follow-up of this study and other confirmatory studies are required before definitive conclusions may be made.

The guideline includes specific representative doses and schedules for the recommended adjuvant chemotherapy regimens (BINV-F).

The guidelines include a footnote stating that women with functioning ovaries and lymph node-negative or lymph node-positive, hormone receptor-positive, invasive breast cancer experience reductions in the risk of recurrence and death from the use of radiation or surgical ovarian ablation or chemical suppression of the ovaries equivalent to the risk reductions achieved with CMF chemotherapy.[103-105] Therefore, surgical or radiation ablation or chemical suppression of the ovaries may be considered an option in these women.

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 CT scan (category 2B), chest x-ray, pathology review, prechemotherapy determination of tumor ER/PR receptor status and HER-2 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)

The new AJCC staging system for breast cancer uses similar clinical staging criteria as previous versions of the staging system. However, the pathologic staging criteria for assigning regional lymph node status (pN stage) differ qualitatively and quantitatively from previous versions of the staging system. For the definition of locally advanced breast cancer used in these guidelines and for the determination of operability, clinical staging of the tumor, especially clinical staging of lymph node status, is required. 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.[106] 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.

A third treatment option that uses high-dose breast and regional lymph node irradiation alone after preoperative chemotherapy generated considerable disagreement among the panel (category 3). The recommendation was included, however, because limited experience at selected institutions suggests high-dose breast and regional lymph node irradiation may provide long-term local control and survival equivalent to surgery plus breast and regional node irradiation.[107]

Patients with an inoperable stage III tumor whose disease progresses 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.[108-110]

In addition, the panel notes no evidence to support the use of "tumor markers" for breast cancer, and routine bone scans in the asymptomatic patient provide no advantage in survival or ability to palliate recurrent disease and are, therefore, not recommended.[111]

Because of the risk of tamoxifen-associated endometrial carcinoma in postmenopausal women, the panel recommends that women with intact uteri who are taking tamoxifen should have yearly pelvic examinations and a rapid evaluation of any vaginal spotting that might occur. 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.

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 recommendation for monitoring of bone health has been added to the current guideline during surveillance.[112]

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 radiograph, bone scan, radiographs of any long or weight-bearing bones or bones that appear abnormal on bone scan, consideration of CT or MRI scan of chest and abdomen, biopsy documentation of first recurrence if possible, and determination of hormone receptor status (estrogen receptor and progesterone receptor) and HER-2 status by IHC or FISH if not previously performed. Positron emission tomography (PET) scanning was added to the current guideline as

NCCN®

Practice Guidelines in Oncology – v.2.2005

Breast Cancer

Guidelines Index
Breast Cancer TOC
Staging, MS, References

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.[113]

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.

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).[114-119]

Bisphosphonates are given in addition to chemotherapy or endocrine therapy. Zoledronic acid may be superior to pamidronate in lytic breast metastasis.[120,121]

Women considered to be appropriate candidates for initial endocrine therapy for recurrent or metastatic disease include those whose tumors are estrogen- or progesterone-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.[122,123] 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.[124-128] 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.[129]

Many premenopausal and postmenopausal women with hormone-responsive breast cancer benefit from sequential endocrine therapy 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 (BINV-H). 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,[130,131] and a recent reanalysis of these studies suggests a longer duration of response favoring fulvestrant.[132] Endocrine therapies in postmenopausal women include selective, nonsteroidal aromatase inhibitors (anastrozole and letrozole); steroidal aromatase inhibitors (exemestane); pure anti-estrogens (fulvestrant); progestins (megestrol acetate); androgens (fluoxymesterone); and high-dose estrogen (ethinyl estradiol). In premenopausal women, therapies include LHRH agonists (goserelin); surgical or radiotherapeutic oophorectomy; progestins (megestrol acetate); androgens (fluoxymesterone); and high-dose estrogen (ethinyl estradiol). After second line hormonal therapy, little high-level evidence exits to assist in selecting the optimal sequence of hormonal therapy.

Women with estrogen and progesterone receptor-negative tumors, symptomatic visceral metastasis, or hormone refractory disease should receive chemotherapy. A variety of chemotherapy regimens are felt to be appropriate, as outlined in the treatment algorithm (BINV-I). The panel finds little compelling evidence that combination chemotherapy is superior to sequential single agents. 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 (BINV-I).

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

by FISH amplified.[32,34,35] Patients with tumors IHC 0 or 1+ for HER2/*neu* or FISH not amplified have very low rates of trastuzumab response, and therapy with trastuzumab is not warranted. Adequate standardization 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.[20,21]

In patients with metastatic or recurrent breast cancer whose tumors overexpress HER2/*neu*, trastuzumab as a single agent[29,31] or in combination with selected chemotherapeutics[30] may be considered. A single randomized trial demonstrates benefit from adding trastuzumab to paclitaxel chemotherapy in patients with IHC 2+ or 3+ for HER2/*neu.* Early 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 is too high for use of this combination outside the confines of a prospective clinical trial.[30,133] The current guideline includes doses and schedules of representative chemotherapy single agents and regimens for use in combination with trastuzumab for metastatic breast cancer (BINV-I).

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).

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.

References

1. Jemal A, Tiwari RC, Murray T et al. Cancer statistics, 2004. CA Cancer J Clin 2004;54(1):8-29.

2. Greene F, Page D, Fleming I et al. AJCC Cancer Staging Mannual. New York: Springer-Verlag; 2002.

3. Singletary SE, Allred C, Ashley P et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol 2002;20(17):3628-3636.

4. Singletary SE, Greene FL, Sobin LH. Classification of isolated tumor cells: clarification of the 6th edition of the American Joint Committee on Cancer Staging Manual. Cancer 2003;98(12):2740-2741.

5. White J, Morrow M, Moughan J et al. Compliance with breast-conservation standards for patients with early-stage breast carcinoma. Cancer 2003;97(4):893-904.

6. Wilkinson NW, Shahryarinejad A, Winston JS et al. Concordance with breast cancer pathology reporting practice guidelines. J Am Coll Surg 2003;196(1):38-43.

7. Rosai J. Borderline epithelial lesions of the breast. Am J Surg Pathol 1991;15(3):209-221.

8. Schnitt SJ, Connolly JL, Tavassoli FA et al. Interobserver reproducibility in the diagnosis of ductal proliferative breast lesions using standardized criteria. Am J Surg Pathol 1992;16(12):1133-1143.

9. Haagensen CD, Haagensen DE, Bodian C. Breast carcinoma: risk and detection. Philadelphia: Saunders; 1981.

10. Bradley SJ, Weaver DW, Bouwman DL. Alternatives in the surgical management of in situ breast cancer. A meta-analysis of outcome. Am Surg 1990;56(7):428-432.

11. Fisher B, Costantino JP, Wickerham DL et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90(18):1371-1388.

12. Fisher B, Dignam J, Wolmark N et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. J Clin Oncol 1998;16(2):441-452.

13. Julien JP, Bijker N, Fentiman IS et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet 2000;355(9203):528-533.

14. Silverstein MJ, Lagios MD, Craig PH et al. A prognostic index for ductal carcinoma in situ of the breast. Cancer 1996;77(11):2267-2274.

15. Silverstein MJ, Lagios MD, Groshen S et al. The influence of margin width on local control of ductal carcinoma in situ of the breast. N Engl J Med 1999;340(19):1455-1461.

16. Tan-Chiu E, Costantino J, Wang J et al. The effect of tamoxifen on benign breast disease. Findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT). Breast Cancer Research and Treatment 2001;69(Abstract 7):210.

17. Tamoxifen for early breast cancer: an overview of the

REF-1

randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998;351(9114):1451-1467.

18. Fisher B, Dignam J, Wolmark N et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet 1999;353(9169):1993-2000.

19. Allred D, Bryant J, Land S et al. Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: Findings from NSABP Protocol B-24. 25th Annual San Antonio Breast Cancer Symposium. 2002(Abstract 30).

20. Roche PC, Suman VJ, Jenkins RB et al. Concordance between local and central laboratory HER2 testing in the breast intergroup trial N9831. J Natl Cancer Inst 2002;94(11):855-857.

21. Paik S, Bryant J, Tan-Chiu E et al. Real-world performance of HER2 testing--National Surgical Adjuvant Breast and Bowel Project experience. J Natl Cancer Inst 2002;94(11):852-854.

22. Press MF, Slamon DJ, Flom KJ et al. Evaluation of HER-2/neu gene amplification and overexpression: comparison of frequently used assay methods in a molecularly characterized cohort of breast cancer specimens. J Clin Oncol 2002;20(14):3095-3105.

23. Pauletti G, Dandekar S, Rong H et al. Assessment of methods for tissue-based detection of the HER-2/neu alteration in human breast cancer: a direct comparison of fluorescence in situ hybridization and immunohistochemistry. J Clin Oncol 2000;18(21):3651-3664.

24. Cooke T, Reeves J, Lanigan A et al. HER2 as a prognostic and predictive marker for breast cancer. Ann Oncol 2001;12 Suppl 1:S23-28.

25. Paik S, Bryant J, Park C et al. erbB-2 and response to doxorubicin in patients with axillary lymph node-positive, hormone receptor-negative breast cancer. J Natl Cancer Inst 1998;90(18):1361-1370.

26. Paik S, Bryant J, Tan-Chiu E et al. HER2 and choice of adjuvant chemotherapy for invasive breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-15. J Natl Cancer Inst 2000;92(24):1991-1998.

27. Piccart MJ, Di Leo A, Hamilton A. HER2, a 'predictive factor' ready to use in the daily management of breast cancer patients? Eur J Cancer 2000;36(14):1755-1761.

28. Thor AD, Berry DA, Budman DR et al. erbB-2, p53, and efficacy of adjuvant therapy in lymph node-positive breast cancer. J Natl Cancer Inst 1998;90(18):1346-1360.

29. Cobleigh MA, Vogel CL, Tripathy D et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999;17(9):2639-2648.

30. Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344(11):783-792.

31. Vogel C, Cobleigh MA, Tripathy D et al. First-line, single-agent Herceptin(R) (trastuzumab) in metastatic breast cancer. a preliminary report. Eur J Cancer 2001;37 Suppl 1:25-29.

32. Field AS, Chamberlain NL, Tran D et al. Suggestions for HER-2/neu testing in breast carcinoma, based on a comparison of

immunohistochemistry and fluorescence in situ hybridisation. Pathology 2001;33(3):278-282.

33. Lebeau A, Deimling D, Kaltz C et al. Her-2/neu analysis in archival tissue samples of human breast cancer: comparison of immunohistochemistry and fluorescence in situ hybridization. J Clin Oncol 2001;19(2):354-363.

34. Tubbs RR, Pettay JD, Roche PC et al. Discrepancies in clinical laboratory testing of eligibility for trastuzumab therapy: apparent immunohistochemical false-positives do not get the message. J Clin Oncol 2001;19(10):2714-2721.

35. Wang S, Saboorian MH, Frenkel E et al. Laboratory assessment of the status of Her-2/neu protein and oncogene in breast cancer specimens: comparison of immunohistochemistry assay with fluorescence in situ hybridisation assays. J Clin Pathol 2000;53(5):374-381.

36. Arriagada R, Le MG, Rochard F et al. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institut Gustave-Roussy Breast Cancer Group. J Clin Oncol 1996;14(5):1558-1564.

37. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. Early Breast Cancer Trialists' Collaborative Group. N Engl J Med 1995;333(22):1444-1455.

38. Fisher B, Anderson S, Bryant J et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347(16):1233-1241.

39. Veronesi U, Cascinelli N, Mariani L et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with

radical mastectomy for early breast cancer. N Engl J Med 2002;347(16):1227-1232.

40. Hughes KS, Schnaper LA, Berry D et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med 2004;351(10):971-977.

41. Fyles AW, McCready DR, Manchul LA et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med 2004;351(10):963-970.

42. Recht A, Come SE, Henderson IC et al. The sequencing of chemotherapy and radiation therapy after conservative surgery for early-stage breast cancer. N Engl J Med 1996;334(21):1356-1361.

43. Abner AL, Recht A, Vicini FA et al. Cosmetic results after surgery, chemotherapy, and radiation therapy for early breast cancer. Int J Radiat Oncol Biol Phys 1991;21(2):331-338.

44. Dubey A, Recht A, Come SE et al. Concurrent CMF and radiation therapy for early stage breast cancer: results of a pilot study. Int J Radiat Oncol Biol Phys 1999;45(4):877-884.

45. Markiewicz DA, Schultz DJ, Haas JA et al. The effects of sequence and type of chemotherapy and radiation therapy on cosmesis and complications after breast conservation therapy. Int J Radiat Oncol Biol Phys 1996;35(4):661-668.

46. Axelsson CK, Mouridsen HT, Zedeler K. Axillary dissection of level I and II lymph nodes is important in breast cancer classification. The Danish Breast Cancer Cooperative Group (DBCG). Eur J Cancer 1992;28A(8-9):1415-1418.

47. Kiricuta CI, Tausch J. A mathematical model of axillary lymph node involvement based on 1446 complete axillary dissections in

patients with breast carcinoma. Cancer 1992;69(10):2496-2501.

48. Bass SS, Lyman GH, McCann CR et al. Lymphatic Mapping and Sentinel Lymph Node Biopsy. Breast J 1999;5(5):288-295.

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

50. Cox CE, Nguyen K, Gray RJ et al. Importance of lymphatic mapping in ductal carcinoma in situ (DCIS): why map DCIS? Am Surg 2001;67(6):513-519; discussion 519-521.

51. Krag D, Weaver D, Ashikaga T et al. The sentinel node in breast cancer--a multicenter validation study. N Engl J Med 1998;339(14):941-946.

52. McMasters KM, Giuliano AE, Ross MI et al. Sentinel-lymph-node biopsy for breast cancer--not yet the standard of care. N Engl J Med 1998;339(14):990-995.

53. O'Hea BJ, Hill AD, El-Shirbiny AM et al. Sentinel lymph node biopsy in breast cancer: initial experience at Memorial Sloan-Kettering Cancer Center. J Am Coll Surg 1998;186(4):423-427.

54. Veronesi U, Paganelli G, Galimberti V et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. Lancet 1997;349(9069):1864-1867.

55. Dupont E, Cox C, Shivers S et al. Learning curves and breast cancer lymphatic mapping: institutional volume index. J Surg Res 2001;97(1):92-96.

56. Fisher B, Redmond C, Fisher ER et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med 1985;312(11):674-681.

57. Fisher B, Bryant J, Wolmark N et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998;16(8):2672-2685.

58. Semiglazov V, Semiglazov VV, Ivanov VG et al. Anastrazole (A) vs tamoxifen (T) vs combine (A+T) as neoadjuvant endocrine therapy of postmenopausal breast cancer patients. Proc Am Soc Clin Oncol 2003;22:880 (abstr 3538).

59. Smith I. Comparison of anastrozole vs tamoxifen alone and in combination as neoadjuvant treatment of estrogen receptor positive (ER+) operable breast cancer in postmenopausal women: the IMPACT trial. 26th Annual San Antonio Breast Cancer Symposium. 2003:Abstract 1.

60. Ellis MJ, Coop A, Singh B et al. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol 2001;19(18):3808-3816.

61. Hellman S. Stopping metastases at their source. N Engl J Med 1997;337(14):996-997.

62. Overgaard M, Hansen PS, Overgaard J et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 1997;337(14):949-955.

63. Overgaard M, Jensen MB, Overgaard J et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 1999;353(9165):1641-1648.

64. Ragaz J, Jackson SM, Le N et al. Adjuvant radiotherapy and

chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 1997;337(14):956-962.

65. Recht A, Edge SB, Solin LJ et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001;19(5):1539-1569.

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

67. Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998;352(9132):930-942.

68. Loprinzi CL, Thome SD. Understanding the utility of adjuvant systemic therapy for primary breast cancer. J Clin Oncol 2001;19(4):972-979.

69. Ravdin PM, Siminoff LA, Davis GJ et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. J Clin Oncol 2001;19(4):980-991.

70. Berry DA, Muss HB, Thor AD et al. HER-2/neu and p53 expression versus tamoxifen resistance in estrogen receptor-positive, node-positive breast cancer. J Clin Oncol 2000;18(20):3471-3479.

71. Eppenberger-Castori S, Kueng W, Benz C et al. Prognostic and predictive significance of ErbB-2 breast tumor levels measured by enzyme immunoassay. J Clin Oncol 2001;19(3):645-656.

72. Knoop AS, Bentzen SM, Nielsen MM et al. Value of epidermal growth factor receptor, HER2, p53, and steroid receptors in

predicting the efficacy of tamoxifen in high-risk postmenopausal breast cancer patients. J Clin Oncol 2001;19(14):3376-3384.

73. Mass R. The role of HER-2 expression in predicting response to therapy in breast cancer. Semin Oncol 2000;27(6 Suppl 11):46-52; discussion 92-100.

74. Pegram MD, Pauletti G, Slamon DJ. HER-2/neu as a predictive marker of response to breast cancer therapy. Breast Cancer Res Treat 1998;52(1-3):65-77.

75. Baum M, Budzar AU, Cuzick J et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet 2002;359(9324):2131-2139.

76. Baum M, Buzdar A, Cuzick J et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. Cancer 2003;98(9):1802-1810.

77. Dowsett M. Analysis of time to recurrence in the ATAC (arimidex, tamoxifen, alone or in combination) trial according to estrogen receptor and progesterone receptor status. 26th Annual San Antonio Breast Cancer Symposium. 2003:Abstract 4.

78. Duffy S, Jackson T. On behalf of the ATAC Trialists' Group. The ATAC ('Arimidex', tamoxifen, alone or in combination) early breast cancer (EBC) trial in postmenopausal (PM) patients: endometrial sub-protocol results. Proc Am Soc Clin Oncol. 2002;21(Abstract 158):40a.

79. Fallowfield I, Cella D. Assessing the quality of life (QOL) of postmenopausal (PM) women randomized into the ATAC ('Arimidex', tamoxifen, alone or in combination) adjuvant breast cancer (BC) trial. Proc Am Soc Clin Oncol. 2002;21(Abstract 159):40a.

80. Dowsett M, Cuzick J, Howell A et al. Pharmacokinetics of anastrozole and tamoxifen alone, and in combination, during adjuvant endocrine therapy for early breast cancer in postmenopausal women: a sub-protocol of the 'Arimidex and tamoxifen alone or in combination' (ATAC) trial. Br J Cancer 2001;85(3):317-324.

81. Boccardo F, Rubagotti A, Amoroso D et al. Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment. Paper presented at: 26th Annual San Antonio Breast Cancer Symposium, 2003; San Antonio, TX.

82. Coombes RC, Hall E, Gibson LJ et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350(11):1081-1092.

83. Goss PE, Ingle JN, Martino S et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003;349(19):1793-1802.

84. Swain SM, Wilson JW, Mamounas EP et al. Estrogen receptor status of primary breast cancer is predictive of estrogen receptor status of contralateral breast cancer. J Natl Cancer Inst 2004;96(7):516-523.

85. Albain K, Green S, Ravdin P et al. Adjuvant chemohormonal therapy for primary breast cancer should be sequential instead of concurrent: initial results from intergroup trial 0100 (SWOG-8814). Proc Am Soc Clin Oncol 2002;21(Abstract 143):37a.

86. Wood WC, Budman DR, Korzun AH et al. Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. N Engl J Med 1994;330(18):1253-1259.

87. Menard S, Valagussa P, Pilotti S et al. Response to cyclophosphamide, methotrexate, and fluorouracil in lymph node-positive breast cancer according to HER2 overexpression and other tumor biologic variables. J Clin Oncol 2001;19(2):329-335.

88. Muss HB, Thor AD, Berry DA et al. c-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer. N Engl J Med 1994;330(18):1260-1266.

89. Pritchard K, O'Malley F, Andrulis I et al. Prognostic and predictive value of HER2/neu in a randomized trial comparing CMF to CEF in premenopausal women with axillary lymph node positive breast cancer (NCIC CTG MA.5). Proc Am Soc Clin Oncol 2002;21(Abstract 165).

90. Bang SM, Heo DS, Lee KH et al. Adjuvant doxorubicin and cyclophosphamide versus cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy in premenopausal women with axillary lymph node positive breast carcinoma. Cancer 2000;89(12):2521-2526.

91. Fisher B, Anderson S, Tan-Chiu E et al. Tamoxifen and chemotherapy for axillary node-negative, estrogen receptor-negative breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-23. J Clin Oncol 2001;19(4):931-942.

92. Fisher B, Brown AM, Dimitrov NV et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction

therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. J Clin Oncol 1990;8(9):1483-1496.

93. Fisher B, Anderson S, Wickerham DL et al. Increased intensification and total dose of cyclophosphamide in a doxorubicin-cyclophosphamide regimen for the treatment of primary breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-22. J Clin Oncol 1997;15(5):1858-1869.

94. Henderson IC, Berry DA, Demetri GD et al. Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 2003;21(6):976-983.

95. Bonadonna G, Zambetti M, Valagussa P. Sequential or alternating doxorubicin and CMF regimens in breast cancer with more than three positive nodes. Ten-year results. JAMA 1995;273(7):542-547.

96. Silvestrini R, Luisi A, Zambetti M et al. Cell proliferation and outcome following doxorubicin plus CMF regimens in node-positive breast cancer. Int J Cancer 2000;87(3):405-411.

97. Mamounas E, Bryant J, Lembersky B et al. Paclitaxel (T) following doxorubicin/cyclophosphamide (AC) as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28. Proc Am Soc Clin Oncol 2003;22(Abstract 12):4.

98. Citron ML, Berry DA, Cirrincione C et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21(8):1431-1439.

99. Levine MN, Bramwell VH, Pritchard KI et al. Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1998;16(8):2651-2658.

100. French Adjvuant Study Group. Benefit of a high-dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French Adjuvant Study Group 05 randomized trial. J Clin Oncol 2001;19(3):602-611.

101. Piccart MJ, Di Leo A, Beauduin M et al. Phase III trial comparing two dose levels of epirubicin combined with cyclophosphamide with cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. J Clin Oncol 2001;19(12):3103-3110.

102. Nabholtz JM, Cantin J, Chang J et al. Phase III trial comparing granulocyte colony-stimulating factor to leridistim in the prevention of neutropenic complications in breast cancer patients treated with docetaxel/doxorubicin/cyclophosphamide: results of the BCIRG 004 trial. Clin Breast Cancer 2002;3(4):268-275.

103. Boccardo F, Rubagotti A, Amoroso D et al. Cyclophosphamide, methotrexate, and fluorouracil versus tamoxifen plus ovarian suppression as adjuvant treatment of estrogen receptor-positive pre-/perimenopausal breast cancer patients: results of the Italian

Breast Cancer Adjuvant Study Group 02 randomized trial. boccardo@hp380.ist.unige.it. J Clin Oncol 2000;18(14):2718-2727.

104. Ovarian ablation in early breast cancer: overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1996;348(9036):1189-1196.

105. Jakesz R, Hausmaninger H, Kubista E et al. Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer--Austrian Breast and Colorectal Cancer Study Group Trial 5. J Clin Oncol 2002;20(24):4621-4627.

106. Hotobagyi G, Singletary S, Strom E. Treatment of locally advanced and inflammatory breast cancer. In: Harris J, ed. Diseases of the breast. Philadelphia: Lippincott Williams and Wilkins; 2000.

107. Favret AM, Carlson RW, Goffinet DR et al. Locally advanced breast cancer: is surgery necessary? Breast J 2001;7(2):131-137.

108. Rosselli Del Turco M, Palli D, Cariddi A et al. Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. National Research Council Project on Breast Cancer follow-up. JAMA 1994;271(20):1593-1597.

109. Smith TJ, Davidson NE, Schapira DV et al. American Society of Clinical Oncology 1998 update of recommended breast cancer surveillance guidelines. J Clin Oncol 1999;17(3):1080-1082.

110. Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. The GIVIO Investigators. JAMA 1994;271(20):1587-1592.

111. Bast RC, Jr., Ravdin P, Hayes DF et al. 2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001;19(6):1865-1878.

112. Hillner BE, Ingle JN, Chlebowski RT et al. American Society of Clinical Oncology 2003 Update on the Role of Bisphosphonates and Bone Health Issues in Women With Breast Cancer. J Clin Oncol 2003;21(21):4042-4057.

113. Wahl RL. Current status of PET in breast cancer imaging, staging, and therapy. Semin Roentgenol 2001;36(3):250-260.

114. Conte PF, Latreille J, Mauriac L et al. Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial. The Aredia Multinational Cooperative Group. J Clin Oncol 1996;14(9):2552-2559.

115. Hortobagyi GN, Theriault RL, Lipton A et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. J Clin Oncol 1998;16(6):2038-2044.

116. Theriault RL, Lipton A, Hortobagyi GN et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. J Clin Oncol 1999;17(3):846-854.

117. Berenson JR, Rosen LS, Howell A et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. Cancer 2001;91(7):1191-1200.

118. Ali SM, Esteva FJ, Hortobagyi G et al. Safety and efficacy of

bisphosphonates beyond 24 months in cancer patients. J Clin Oncol 2001;19(14):3434-3437.

119. Hillner BE, Ingle JN, Berenson JR et al. American Society of Clinical Oncology guideline on the role of bisphosphonates in breast cancer. American Society of Clinical Oncology Bisphosphonates Expert Panel. J Clin Oncol 2000;18(6):1378-1391.

120. Rosen LS, Gordon DH, Dugan W, Jr. et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer 2004;100(1):36-43.

121. Rosen LS, Gordon D, Kaminski M et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. Cancer J 2001;7(5):377-387.

122. Buzdar A, Douma J, Davidson N et al. Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. J Clin Oncol 2001;19(14):3357-3366.

123. Buzdar AU, Jonat W, Howell A et al. Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma: results of a survival update based on a combined analysis of data from two mature phase III trials. Arimidex Study Group. Cancer 1998;83(6):1142-1152.

124. Bonneterre J, Thurlimann B, Robertson JF et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. J Clin Oncol 2000;18(22):3748-3757.

125. Mouridsen H, Gershanovich M, Sun Y et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol 2001;19(10):2596-2606.

126. Nabholtz JM, Buzdar A, Pollak M et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. J Clin Oncol 2000;18(22):3758-3767.

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

128. Paridaens R, Therasse P, Dirix L et al. First line hormonal treatment (HT) for metastatic breast cancer (MBC) with exemestane (E) or tamoxifen (T) in postmenopausal patients (pts) A randomized phase III trial of the EORTC Breast Group. Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition) 2004;22(14S):515.

129. Klijn JG, Blamey RW, Boccardo F et al. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol 2001;19(2):343-353.

130. Osborne CK, Pippen J, Jones SE et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast

cancer progressing on prior endocrine therapy: results of a North American trial. J Clin Oncol 2002;20(16):3386-3395.

131. Howell A, Robertson JF, Quaresma Albano J et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. J Clin Oncol 2002;20(16):3396-3403.

132. Parker L, Webster A. Greater duration of response in patients receiving fulvestrant ('Faslodex') compared with those receiving anastrozole ('Arimidex'). Proc Am Soc Clin Oncol 2002;21(Abstract 160):41a.

133. Seidman A, Hudis C, Pierri MK et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 2002;20(5):1215-1221.