National
Comprehensive
Cancer
Network

Clinical Practice Guidelines in Oncology – v.1.2003

Continue

Breast Cancer

NCCN Breast Cancer Panel Members

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

* Benjamin O. Anderson, MD
University of Washington Medical Center

William Bensinger, MD
Fred Hutchinson Cancer Research Center

Harold Burstein, MD, PhD
Dana-Farber Cancer Institute

Charles E. Cox, 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

Clifford Hudis, MD
Memorial Sloan-Kettering Cancer Center

Britt-Marie Ljung, MD
UCSF Comprehensive Cancer Center

Larry 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 University of Nebraska Medical Center

Edibaldo Silva, MD, PhD
St. JudeChildren's Research Hospital/University of Tennessee Health Services

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

Mary Lou Smith
Consultant

George Somlo, MD
City of Hope Cancer Center

Richard Theriault, DO, MBA
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 Cancer Institute

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

Continue

* Writing Committee member

For help using these documents, please click here

Guidelines Index

Print the Breast Cancer Guideline

Order the Patient Version of the Breast Cancer Guideline

Staging

Manuscript

References

t Treatmen BINV-4

Preoperative Chemotherapy Guideline

› Clinical Stage IIA, IIB, Work-Up (BINV-6)

IIIA IIIB T3 N1

›

- Surveillance/Follow-Up, Recurrence Work-Up or Initial Work-up for Stage IV Disease (BINV-11)
- Treatment of Recurrence/Stage IV Disease (BINV-12)
- Surgical Axillary Staging - Stage I, IIA, and IIB (BINV-A)
- Axillary Dissection (BINV-B)
-
- Adjuvant Hormonal Therapy (BINV-D)
- Adjuvant Chemotherapy (BINV-E)
- Subsequent Hormonal Therapy (BINV-F)
-

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

See NCCN Categories of Consensus

[a]See NCCN Breast Cancer Screening and Diagnosis 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.

Noninvasive Breast C

DIAGNOSIS	WORK-UP		FINDINGS	
Ductal carcinoma in situ Stage 0 Tis (DCIS), N0, M0	• H&P • Diagnostic bilateral mammogram • Pathology review	Excisional biopsy[b]	Widespread disease (2 or more quadrants)	
			Margins positive[b,c]	See Primary Treatment (BNON-3)
			Margins negative[b,c]	

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

[c]See margin status in DCIS (BNON-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.

Noninvasive Breast Cancer

FINDINGS	PRIMARY TREATMENT
Widespread disease (2 or more quadrants)	**Total mastectomy without lymph node dissection[j] ± reconstruction[g]**
Margins positive[b]	**Excision[j] + RT [d,e,f,g,h,i]** **or** **Total mastectomy without lymph node dissection[j] ± reconstruction[e,g]**
Margins negative[b,c]	**See Postsurgical Treatment (BNON-4)**
Small (< 0.5 cm), unicentric, low grade →	**Excision[j] + RT [d,e,f,g,h,i]** **or** **Total mastectomy without lymph node dissection[j] ± reconstruction[e,g]** → **or** **Excision alone (category 2B)[f,g,h,i,j]**

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

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

[d]Whole breast irradiation with boost (by photons, brachytherapy or electron beam) to tumor bed. Boost to tumor bed is especially encouraged in those 50y of age or younger.

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

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

[g]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.

[h]See Contraindications to Breast-Conserving Therapy (BINV-C).

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

[j]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

Noninvasive Breast C

DCIS POSTSURGICAL TREATMENT

Adjuvant treatment:
Consider tamoxifen for 5 years for:
- **Patients treated with breast-conserving therapy (lumpectomy) and RT (category 1)[k]**
- **Patients treated with excision alone [k]**

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

SURVEILLANCE/F

- **Interval history**
  for 5 yr, then an
- **Mammogram ev**
- **If treated with ta**
  Breast Cancer R

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

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

Noninvasive Breast C

Margin Status in DCIS

Substantial controversy exists regarding the definition of a negativ margin in DCIS. Controversy arises out of the heterogeneity of the in distinguishing the spectrum of hyperplastic conditions, anatomi the location of the margin, and inadequate prospective data on pro DCIS. Margins greater than 10 mm are widely accepted as negativ and may lead to a less optimal cosmetic outcome). Margins less th are considered inadequate. There are insufficient data to make defi regarding margins between 1 and 10 mm.

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.

Invasive Breast Canc

CLINICAL STAGE	WORK-UP
Stage I T1, N0, M0 or Stage IIA T0, N1, M0 T1, N1, M0 T2, N0, M0 or Stage IIB T2, N1, M0 T3, N0, M0 or T3, N1, M0	• H&P • CBC, platelets • Liver function tests • Chest x-ray • Diagnostic bilateral mammogram, ultrasound as nec • Pathology review • Determination of tumor ER/PR status and HER-2 stat • Breast MRI with dedicated breast coil for cases equi breast conserving therapy (optional) • Bone scan (optional) (Indicated if localized symptom elevated alkaline phosphatase or if T3, N1, M0) (categ • Abdominal CT or US or MRI (optional for stage IIA or indicated if elevated alkaline phosphatase or if T3, N (category 2B)

See Locoregional Treatment (BINV-2)

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

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

LOCOREGIONAL TREATMENT OF CLINIC

	≥ 4 positive nodes[d]	
Lumpectomy, level I, II axillary dissection[b,c]	1-3 positive nodes	See Systemic Adjuvant Treatment (BINV-4)
or	Negative nodes	
Total mastectomy with level I,II axillary dissection[b] (category 1) ± reconstruction		See BINV-3
or		
If T2 or T3 and fulfills criteria for breast conserving therapy except for size		Consider Preoperative Chemotherapy Guideline (BINV-6)

[b] See Surgical Axillary Staging (BINV-A) and Axillary Dissection (BINV-B).

[c] See Contraindications to Breast-Conserving Therapy (BINV-C).

[d] Consideration may be given to additional staging including bone scan and abdominal CT/US/MRI; chest CT 2B

[e] If internal mammary lymph nodes are clinically or patholgically positive, RT should be given to the internal mammary node field, otherwise the treatment to the internal mammary field 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.

Invasive Breast Cancer

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

Total mastectomy with level I,II axillary dissection[b] (category 1) ± reconstruction	≥ 4 positive nodes[d]	Postchemotherapy RT to chest wall + supraclavicular area[e] (category 1); consider internal mammary node RT (category 3; controversy is "no RT" vs "consider for internal mammary nodes")
	1-3 positive nodes	Consider postchemotherapy RT to chest wall + supraclavicular area[e] (category 1)[f]; if RT is given, consider internal mammary RT (category 3; controversy is "no RT" vs "consider for internal mammary nodes")
	Tumor > 5 cm or margins positive	Postchemotherapy RT to chest wall
	Negative nodes and tumor ≤ 5 cm and margins close (< 1mm) →	Consider RT to chest wall
	Negative nodes and tumor ≤ 5 cm and margins ≥ 1mm →	No RT

[b] See Surgical Axillary Staging (BINV-A) and Axillary Dissection (BINV-B).

[d] Consideration may be given to additional staging including bone scan; abdominal CT/US/MRI; chest CT (category 2B).

[e] If internal mammary lymph nodes are clinically or patholgically positive, RT should be given to the internal mammary node field, otherwise the treatment to the internal mammary field 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.

[f] There is contradictory high-level evidence on survival benefit in this subset and risk of local recurrence is low in the absence of RT.

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

Prac
in O

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

Node positive (one or more metastasis >2 mm to one or more ipsilateral axillary lymph nodes) → See BINV-5

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

See Follow-Up (BINV-11)

[g] Angiolymphatic invasion, high nuclear grade, high histologic grade, HER-2 overexpression, hormone receptor negative (category 2B).

[h] If ER+ consider tamoxifen for risk reduction and to diminish the small risk of disease recurrence.

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

[j] Chemotherapy and tamoxifen used as adjuvant therapy should be given sequentially with tamoxifen following chemotherapy.The benefits of chemotherapy and of tamoxifen are additive. However, the absolute benefit from chemotherapy may be small. The decision to add chemotherapy to tamoxifen should be individualized, especially in those with a favorable prognosis and in older women where the incremental benefit of ch m be small

ablation/suppression in premenopausal women who have received adjuvant chemotherapy is uncertain.

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

Invasive Breast Cancer

SYSTEMIC ADJUVANT TREATMENT

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

Hormone-receptor negative → **Adjuvant chemotherapy[i] (category 1)** → See Follow-Up

Hormone-receptor positive → **Tamoxifen, 20 mg/d for 5 years[l] + adjuvant chemotherapy [i,j,k]** →

See Adjuvant Hormonal Therapy (BINV-D) and Aduvant Chemotherapy (BINV-E)

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

[j]Chemotherapy and tamoxifen used as adjuvant therapy should be given sequentially with tamoxifen following chemotherapy.The benefits of chemotherapy and of tamoxifen are additive. However, the absolute benefit from chemotherapy may be small. The decision to add chemotherapy to tamoxifen should be individualized, especially in those with a favorable prognosis and in older women where the incremental benefit of chemotherapy may be small.

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

[l]Anastrozole 1mg/d for 5 y may be considered an option to tamoxifen. See Adjuvant Hormonal Therapy (BINV-D)

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

Invasive Breast Canc

Preoperative Chemotherapy Guideline

CLINICAL STAGE	WORK-UP
Stage IIA **T2, N0, M0** **Stage IIB** **T2, N1, M0** **T3, N0, M0** **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** • **Pathology review** • **Determination of tumor ER/PR status and HER-2** • **Breast MRI with dedicated breast coil for cases** (**breast conserving therapy (optional)** • **Bone scan (optional) (Indicated if localized symptoms or elevated alkaline phosphatase or i (category 2B)** • **Abdominal CT or US or MRI (optional for stage II indicated if elevated alkaline phosphatase or if T (category 2B)**

→ See Primary Treatment (BINV-7)

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

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.

Invasive Bre

Preoperative Guideline

PRIMARY TREATMENT

See Mastectomy and level I/II axillary dissection (BINV-8)

Desires breast preservation → **Core biopsy of breast ± FNA of clinically positive lymph node** → **Localization of tumor bed for future surgical management** → **Preoperative chemotherapy**

See Mastectomy and level I/II axillary dissection (BINV-8)

See Lumpectomy with level I/II axillary dissection (BINV-8)

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

[m] A number of combination and single agent chemotherapy regimens have activity in the preoper setting.In general, those chemotherapy regimens recommended in the adjuvant setting (See BIf may be considered in the preoperative setting. Consider preoperative hormonal therapy for patie positive hormone receptors who decline or are not appropriate for cytotoxic chemotherapy (category 2B; for hormonal therapy)

[n] If there is progressive disease after any course of therapy or no response after 3-4 cycles, proce mastectomy.

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.

Invasive Breast Cancer

Preoperative Guideline

PRIMARY TREATMENT → **ADJUVANT TREATMENT**

Mastectomy and level I/II axillary dissection ± reconstruction → **Consider additional chemotherapy** →

- **Chest wall + supraclavicular area RT; consider internal mammary RT[e] (category 3; controversy is "no RT" vs "consider" for internal mammary nodes) (If patient is T2, N0 and pN0 postmastectomy RT is optional)**

and

- **Tamoxifen if ER - positive (category 1)**

See Adjuvant Hormonal Therapy (BINV-D)

→

Lumpectomy with level I/II axillary dissection → **Consider additional chemotherapy** →

- **Breast + supraclavicular area RT[o]; consider internal mammary RT (category 3; controversy is "no RT" vs "consider" for internal mammary nodes)**

and

- **Tamoxifen if ER - positive (category 1)**

See Adjuvant Hormonal Therapy (BINV-D)

[e] If internal mammary lymph nodes are clinically or patholgically positive, RT should be given to the internal mammary node field, otherwise the treatment to the internal mammary field 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.

[o] Whole breast irradiation with boost (by photons, brachytherapy or electron beam) to tumor bed. Boost to tumor bed is especially encouraged in those 50y of age or younger. If internal mammary lymph nodes are clinically or pathologically positive, RT should be given to the internal mammary field, otherwise the treatment to the internal mammary field 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.

N1, M0 disease, see BINV-1)

See Preoperative Chemotherapy and Local-Regional Treatment (BINV-10)

See pathway for Systemic recurrence (BINV-11)

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.

Invasive Breast Canc

PREOPERATIVE CHEMOTHERAPY FOR LOCALLY ADVANCED INVASIVE BREAST CANCER

LOCAL-REGIONAL TREATMENT

ADJUVANT

Anthracycline-based preoperative chemotherapy ± tamoxifen, 20 mg/d for 5 y

Response →

Total mastectomy + level I/II axillary dissection + RT to chest wall and supraclavicular nodes (plus internal mammary nodes if N3) ± delayed cosmetic reconstruction
or
Consider lumpectomy + level I/II axillary dissection + RT to breast and supraclavicular nodes (plus internal mammary nodes if N3)
or
High dose RT alone (category 3)

→

Additiona tamoxifer 5 years if positive (

→ See Follow-Up/ Surveillance (BINV-11)

Response -

No response →

Consider additional systemic chemotherapy and/or preoperative radiation

No respons

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

Invasive Breast Canc

SURVEILLANCE/ FOLLOW-UP

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

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

- H&P
- CBC, platelets
- Liver function tests
- Chest x-ray
- Bone scan
- X-rays of symptomatic bones and long and weight-bearing bones abnormal on bone scan
- Consider CT or MRI of chest and abdomen
- Biopsy documentation of first recurrence, if possible
- If not previously performed, determination of tumor ER/PR and HER-2 status[a]
- Pet scan (optional)(category 2B)

See Treatment of Recurrence/Stage IV (BINV-12)

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

[p]Pamidronate or zoledronic acid (with calcium citrate 500 mg and vitamin D 400 mg 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.

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.

Invasive Breast Cancer

TREATMENT OF RECURRENCE/STAGE IV

Local disease only

- Initial treatment with mastectomy → Surgical resection (if possible) + RT (if possible) → Conside
- Initial treatment with lumpectomy + RT → Mastectomy → Conside

Systemic disease[p]

- ER/PR positive or bone/soft tissue only or asymptomatic visceral
  - Prior antiestrogen within 1 yr → Second-line hormonal therapy[q]
  - No prior antiestrogen or > 1 yr off antiestrogen
    - Postmenopausal → Non-steroidal aromatase inhibitor or Antiestrogen → See (BINV-13)
    - Premenopausal → Antiestrogen ± LHRH agonist →
- ER/PR negative or symptomatic visceral or hormone refractory
  - HER-2[a] over-expressed → Trastuzumab ± chemotherapy[r,s,t]
  - HER-2[a] not over-expressed → Chemotherapy[r] → 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 (e.g., intrathecal methotrexate) indicated for localized clinical scenarios:

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

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

[p]Pamidronate or zoledronic acid (with calcium citrate 500 mg and vitamin D 400 mg supplement) should be given (category1) in addition to chemotherapy or hormonal therapy if bone metastasis present, expected survival ≥ 3 months, and creatinine < 3.0 mg/dL.

[q]See Subsequent Hormonal Therapy (BINV-F).

[s]A single randomized trial is available supporting the addition of trastuzumab to paclitaxel. Early non-randomized data are available supporting the addition of such agents as docetaxel, vinorelbine, and platinum compounds in combination with trastuzumab.

[t]Trastuzumab iven in combination with AC is associated with 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.

Invasive Breast Cancer

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

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

- **Yes** → **Chemotherapy[r] (As in BINV-12)**
- **No** → **Trial of new hormone therapy[q]**

No response to hormonal therapy[u] → **Chemotherapy[r] (As in BINV-12)**

TREATMENT OF RECURRENCE

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

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

[q] See Subsequent Hormonal Therapy (BINV-F).

[u] 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.

Invasive Breast Canc

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 large prior excision in upper, outer quadrant (> 6 cm)**
- **No prior chemotherapy or hormonal therapy**

AND

Experienced sentinel node team[1]

No

Clinically node positive at time of diagnosis

Yes

Clinically node negative at time of diagnosis →

Axillary dissection level I/II

or

Sentinel node mapp and excision[2]

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

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

[3]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 LocoregionalTreatment (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.

Invasive Breast Canc

AXILLARY DISSECTION

In the absence of definitive data demonstrating superior survival fron
axillary lymph node dissection, patients who have particularly favoral
whom the selection of adjuvant systemic therapy is unlikely to be affe
those with serious comorbid conditions, the performance of axillary l
may be considered optional. The axillary dissection should be extend
nodes only if there is gross disease apparent in the level I or II nodes.

Sentinel lymph node biopsy may be considered an option (category 2
experienced sentinel node team and the patient is an appropriate sen
candidate (See BINV-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.

Invasive Breast Canc

CONTRAINDICATIONS TO BREAST-CONSERVING THI REQUIRING RADIATION THERAPY

Contraindications for breast-conserving therapy requiring radiat

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

Relative:
- Multifocal disease requiring two or more separate surgical i
- Active connective tissue disease involving the skin (especia scleroderma and lupus)
- Tumors > 5 cm (category 2B)

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.

Invasive Breast Canc

ADJUVANT HORMONAL THERAPY

- Tamoxifen 20 mg/d for 5y
- Anastrozole 1mg/d for 5y

Early evidence from a single, large, double-blind, randomized cl demonstrates that anastrozole provides superior disease free s favorable toxicity profile compared to tamoxifen as adjuvant the receptor-positive breast cancer in postmenopausal women. Adc this trial and additional experience is required before definitive made. At the current time, anastrozole may be considered as an after discussion of the available data between the physician anc do not address whether women currently on tamoxifen should t anastrozole. Anastrozole is not appropriate therapy for premenc

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

Invasive Breast Cancer

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 CEF (cyclophosphamide/epirubicin/fluorouracil)
- AC (doxorubicin/cyclophosphamide) ± sequential paclitaxel[6]
- EC (epirubicin/cyclophosphamide)
- TAC (docetaxel/doxorubicin/cyclophosphamide)[6]
- A → CMF[7] (doxorubicin followed by cyclophosphamide/methotrexate/fluorouracil)
- CMF (cyclophosphamide/methotrexate/fluorouracil)

[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]Trastuzumab should be used as adjuvant therapy only in the setting of a clinical trial.

[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]Early evidence from a single clinical trial suggests that AC followed by paclitaxel may be superior to AC alone. Early evidence from another single clinical trial suggests that TAC chemotherapy may be superior to FAC.

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

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

SUBSEQUENT HORMONAL THERAPY

(For first-line hormonal therapy see BINV-11)

PREMENOPAUSAL PATIENTS

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

POSTMENOPAUSAL

- Non-steroidal arom (anastrozole, letroz aromatase inactiva
- Fulvestrant
- Tamoxifen or Toren
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol

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.

PREFERRED CHEMOTHERAPY REGIMEN
RECURRENT OR METASTATIC BREAST CA

Preferred Agents	Preferred Combinations
•Anthracyclines •Taxanes •Capecitabine •Vinorelbine	•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

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

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.

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***
1c	Metastasis in 1 to 3 axillary lymph nodes and in internal mammary nodes with sentinel lymph node ((If associated with gr nodes, the internal m to reflect increased t
pN2	Metastasis in 4 to 9 a *apparent** internal ma axillary lymph node n
pN2a	Metastasis in 4 to 9 a deposit greater than
pN2b	Metastasis in *clinicall* nodes in the *absence*
pN3	Metastasis in 10 or m infraclavicular lymph ipsilateral internal ma of 1 or more positive axillary lymph nodes metastasis in interna ipsilateral supraclavi
pN3a	Metastasis in 10 or m tumor deposit greate infraclavicular lymph
pN3b	Metastasis in *clinicall* mammary lymph nod positive axillary lymp lymph nodes and in i microscopic disease dissection but not *cli*
pN3c	Metastasis in ipsilate

* *Clinically apparent* is defined as de lymphoscintigraphy)

** *Not clinically apparent* is defined a (excluding lymphoscintigraphy) or by

Staging continued on next page (ST-3)

Table 1 (continued)

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

STAGE GROUPING

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 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

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 vaue of histologic grade in breast cancer experience from a large study with long-term follow-up. Histopathololgy 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 205,000 new cases of breast cancer will be diagnosed in the United States in the year 2002, and approximately 40,000 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 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 Genetic/Familial High-Risk Assessment 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 (e.g., sentinel node biopsy and immunohistochemistry) and the number of lymph nodes involved as a strong prognostic factor in staging allocation.

The most substantial changes are:

1) Micrometastases are distinguished from isolated tumor cells on the basis of size and histologic evidence of malignant activity.
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, once again, will be 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 T any N3M0 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]

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 how postmenopausal women are treated. 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 ductal carcinoma *in situ* (DCIS) and LCIS (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.[4,5] Therefore, pathology review of all cases is appropriate. Bilateral diagnostic mammography should also be performed to identify the presence of multiple primary tumors and to estimate the extent of the noninvasive lesion.

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 guidelines for invasive carcinoma.

Lobular Carcinoma In Situ

The preferred treatment of pure LCIS is observation alone. Bilateral mastectomy, with or without reconstruction, can be considered in special circumstances. Observation alone is the preferred option for women diagnosed with LCIS because their risk of developing invasive carcinoma is low (approximately 21% over 15 years).[6] The histologies of the invasive carcinomas tend to be favorable, and deaths from these second invasive cancers are unusual in appropriately observed women.[7]

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.[8] 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 Guidelines)

Follow-up of patients with LCIS includes physical examinations every 6 to 12 months for 5 years and then annually. Also, yearly mammography is recommended in patients being treated with observation without bilateral mastectomy.

Ductal Carcinoma In Situ

Patients with DCIS and evidence of widespread disease (i.e., 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, in whom negative margins are achieved with the initial excision or with re-excision, breast-conserving therapy and 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 long-term survival with excision and irradiation. Women treated with mastectomy are appropriate candidates for breast reconstruction. Contraindications to breast-conserving therapy that require RT are listed in the algorithm (BINV-C).

Prospective randomized trials have shown that the addition of breast irradiation to a margin-free excision of pure DCIS decreases rates of in-breast recurrence, but does not affect overall survival.[9,10] Although some non-controlled evidence suggests that selected patients have a low risk of local failure with excision alone without breast irradiation,[11,12] 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 risk of a local failure by approximately 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, determine 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 survival of this disease, 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 (> 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 now 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 or 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 pathology margin status.

Pathologically, DCIS falls between atypical ductal hyperplasia and invasive ductal carcinoma within the spectrum of 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.[8] These data also showed that tamoxifen led to a substantial reduction in the risk of developing benign breast disease.[13] The Early Breast Cancer Trialists' overview analysis showed that, with 5 years of tamoxifen therapy, women with estrogen receptor-positive or receptor-unknown tumors had a 47% reduction in the annual odds of recurrence of invasive breast cancer.[14] 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 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.[15]

Tamoxifen treatment, therefore, may be considered in women with DCIS treated with breast-conserving therapy (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 mammography.

Stage I, IIA, or IIB Invasive Breast Cancer

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

The determination of level of HER2/*neu* expression for all newly diagnosed patients with invasive breast cancer is recommended. HER2/*neu* level of expression is variably 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 few have FDA 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.[16,17] 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.[16,19]

Determining HER2/*neu* expression in the initial work-up is recommended for prognostic purposes in patients with node-negative breast cancer (Category 2B).[20] It also assists in the selection of adjuvant therapy in cases in which retrospective data suggest that doxorubicin-based adjuvant therapy may be superior to nondoxorubicin-based chemotherapy in patients with tumors overexpressing HER2/*neu* (Category 2B),[21,22,23,24] and provides baseline information to be considered should the individual develop recurrent disease requiring consideration of trastuzumab therapy (Category 1).[25,26,27] 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.[28,29,30,31] 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.

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 2A) and abdominal imaging (Category 2B) are considered optional.

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 are medically equivalent primary treatment options (Category 1).[32,33,34,35] If adjuvant chemotherapy is indicated, RT should be given after chemotherapy is completed.[35] Breast-conserving RT may be given concurrent with CMF chemotherapy, but methotrexate should either be withheld during the radiation or limited to no more than 2 doses concurrent with the radiation. The impact of concurrent CMF chemotherapy with RT has been demonstrated to decrease the cosmetic outcome of breast-conserving therapy in some, but not all studies.[37,38,39]

The current version of the NCCN 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). RT is absolutely contraindicated for patients who are pregnant, those who received previous moderate- or high-dose RT to the breast or chest wall, for cases in which diffuse suspicious or malignant-appearing microcalcifications are shown on mammography, and in cases of multicentric disease (ie, disease involving 2 or more quadrants of the breast).

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

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 or 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.[40,41] 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 (Category 2B) in certain circumstances to assess the pathologic status of the axillary lymph nodes.[42,43,44,45,46,47,48] Not all women are candidates for sentinel lymph node biopsy. Appropriate candidates are those for whom an experienced sentinel lymph node team is available.[49] In addition, potential candidates should have clinically negative axillary lymph nodes, a primary tumor less than 5 cm in greatest diameter, no large previous excision (> 6 cm), and no preoperative chemotherapy or hormonal therapy. 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 significance of a lymph node that is negative by hematoxylin and eosin staining but positive by cytokeratin IHC is controversial. 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 in selected patients, but not a mandatory replacement for a level I and II axillary dissection.

Furthermore, in the absence of definitive data demonstrating superior survival 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 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, prechemotherapy biopsies have been limited to core needle biopsy or fine needle aspiration (FNA) cytology. Therefore, the initial biopsy in patients anticipated to receive preoperative chemotherapy should be limited to core or FNA biopsy. In some patients, preoperative chemotherapy given before surgery results in sufficient tumor response that breast-conserving therapy becomes possible. Because complete or near-complete clinical responses are common, the use of percutaneously placed clips into the breast under mammographic or ultrasound guidance or other method of localizing prechemotherapy tumor volume aids in the resection of the original area of tumor postchemotherapy and is encouraged. The results of the NSABP B-18 trial show that breast conservation rates are higher after preoperative chemotherapy.[50] However, preoperative chemotherapy has no demonstrated 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 rates have not yet been reported for B-27, and no difference in 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-E) are appropriate to consider in the preoperative chemotherapy setting.

If the tumor responds to preoperative chemotherapy, lumpectomy plus axillary lymph node dissection may be considered if the patient fills the requirement for breast-conserving therapy. BCS should be followed by individualized chemotherapy such as taxanes (Category 2B) and 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 or 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 T2 N0 M0 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, as well as to the supraclavicular nodes, if indicated.

Three randomized 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.[51,52,53,54,55] 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.[56] 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 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, postchemotherapy 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 routine, postmastectomy, postchemotherapy 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.[33] 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. 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.[57,14] 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 recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, the toxicity of the therapy, and comorbidity.[58,59] 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 hormonal therapy regardless of patient age, lymph node status, or whether or not adjuvant chemotherapy is to be administered.[14] 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.[60,61,62,63,64,65] Given the inconsistency of these data and the favorable toxicity profile of the available hormonal therapies, the panel continues to recommend the use of adjuvant hormonal 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 and with favorable prognostic features.

The most firmly established adjuvant hormonal therapy is tamoxifen for both premenopausal and postmenopausal women.[14] The recent results of the Arimidex, Tamoxifen, Alone or in Combination Trial (ATAC Trial) suggest that anastrozole may be an appropriate adjuvant hormonal therapy in postmenopausal women with hormone receptor-positive breast cancer.[66] With a median of 33.3 months follow-up, results in 9366 postmenopausal women with early breast cancer enrolled in the ATAC Trail demonstrate fewer recurrences (hazard ratio, 0.83; 95% CI, 0.71--0.96; $P = .013$) 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], $P = .005$). 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,[67] no deleterious effect on quality of life,[68] and a small pharmacokinetic interference of unclear significance.[69] Few patients have completed all 5 years of prescribed therapy. Therefore, a longer follow-up is needed to confirm these preliminary results, especially because the full benefits from tamoxifen are not observed before 5 years of therapy.[70] This follow-up will also permit better characterization of the toxicity profile of aromatase inhibitors in the adjuvant setting. As a result of the early results from ATAC, the Guidelines were modified in December 2001 to allow consideration of anastrozole as an option to tamoxifen in postmenopausal women with hormone receptor-positive breast cancer after discussion of the available data between the physician and patient. This issue has also been the subject of an ASCO Technology Assessment with the recommendation that a 5-year course of adjuvant tamoxifen remains the standard therapy for women with hormone receptor-positive breast cancer.[71] Anastrozole must not be used in premenopausal women because it inadequately suppresses ovarian estrogen synthesis.

The NSABP database also showed 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 ineffective strategy to reduce the risk of contralateral breast cancer in patients diagnosed with estrogen receptor-negative tumors.[72] Tamoxifen is also associated with a small risk of uterine sarcoma (0.17 cases per 1000 woman-years), an endometrial cancer with poor prognosis,[73] though the clinical impact of this finding is likely to be small.

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. 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 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 Guideline Panel believes that including medullary carcinoma with other special histology cancers that may not require systemic therapy may not be appropriate. The panel recommends that cases classified as medullary 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, tamoxifen with chemotherapy is recommended (Category 1). Anastrozole may be considered as an option to tamoxifen in postmenopausal women. The use of chemotherapy, tamoxifen, and anastrozole in these subsets of patients must be based on balancing the absolute magnitude of risk reduction expected and the individual patient's willingness to experience toxicity to achieve incremental risk reduction.

Patients with lymph node-positive disease are candidates for chemotherapy and, if also hormone receptor-positive, for the addition of tamoxifen (Category 1). In postmenopausal women, anastrozole may be considered as an option to tamoxifen. 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.[74] Consequently, chemotherapy followed by tamoxifen 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 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.[57] Studies using CAF/FAC (cyclophosphamide, doxorubicin, 5-fluorouracil) chemotherapy have shown that the use of full-dose chemotherapy regimens is important.[75] In the Early Breast Cancer Trialists' overview of polychemotherapy, comparison of anthracycline-containing regimens with CMF showed a 12% further reduction in the annual odds of recurrence ($P = .006$) and an 11% further reduction in the annual odds of death ($P = .02$) with anthracycline-containing regimens.[57] 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 of level of HER2*neu* expression and efficacy of anthracycline-containing versus CMF chemotherapy regimens. Retrospective analysis has suggested that the superiority of anthracycline-containing chemotherapy may be limited to the treatment of those breast cancers that overexpress the HER2/*neu* oncogene.[22,24,63,76,77] This retrospective finding across several clinical trials that doxorubicin-based chemotherapy may be more efficacious in patients whose tumors overexpress HER2/*neu*,[21,22,24,78] 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.[79,80,81] No benefit from dose intensification of either doxorubicin or cyclophosphamide was shown in the published AC series.[82,83] 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.[84,85]

The early results of a randomized trial comparing AC chemotherapy with or without sequential paclitaxel chemotherapy in women with axillary node-positive breast cancer suggest improved disease-free rates and overall survival with the addition of paclitaxel.[86] On retrospective analysis, the apparent advantage of the paclitaxel-containing regimen appears limited primarily to women with estrogen receptor-negative breast cancers. The mature results of both this trial and a trial of similar design from the National Surgical Adjuvant Breast and Bowel Project (NSABP B-28) are required before definitive recommendations can be made.

Two randomized prospective trials of CEF chemotherapy in axillary lymph node-positive breast cancer are available. In one trial, premenopausal women with node-positive breast cancer were randomized to receive classic CMF therapy versus CEF chemotherapy using high-dose epirubicin. Five-year relapse-free survival (63% vs 53%; $P = .009$) and overall survival (77% vs 70%; $P = .03$) both favored the CEF arm of the trial.[87] 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%; $P = .03$) and overall survival (65% vs 76%; $P = .007$) both favored the epirubicin 100 mg/m^2 arm (French Adjuvant Study Group, 2001). A recent trial compared 2 dose levels of EC chemotherapy with CMF chemotherapy in women with node-positive breast cancer.[88] 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 CAF chemotherapy in axillary lymph node-positive breast cancer suggest that TAC is superior to CAF.[89] 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 guidelines include a footnote stating that women younger than age 50 with functioning ovaries and lymph node-negative or lymph node-positive, hormone receptor-positive, invasive breast cancer experience reductions in the risk of recurrence and death from the use of radiation or surgical ovarian ablation or chemical suppression of the ovaries equivalent to the risk reductions achieved with polychemotherapy.[90,91,92] 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 guidelines include a bone scan (Category 2B), chest CT scan (Category 2B), 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 T3, N1, M0 disease versus those who have clinical Tany, N2, M0 disease, based on evaluation by a multidisciplinary team. For patients with operable locally advanced disease, generally patients with clinical T3, N1, M0 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 postsurgical systemic adjuvant therapy 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.[93] 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 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.[94]

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 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.

Surveillance and Follow-up

Posttherapy 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.[95,96,97]

In addition, the panel continues to believe determination of the available "tumor markers" for breast cancer and routine bone scans in the asymptomatic patient provide no advantage in survival or ability to palliate recurrent disease and are, therefore, not recommended.[98]

Because of the risk of tamoxifen-associated endometrial carcinoma in postmenopausal women, the panel does recommend 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.

Stage IV Metastatic or Recurrent Breast Cancer

The staging evaluation of women who present with metastatic or

recurrent breast cancer includes the performance of a CBC, platelet count, liver function tests, chest 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 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.[99]

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. 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 hormonal therapy, as is the case for women with systemic recurrences.

Systemic Disease

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

Women with bony metastasis, especially if lytic, should be given a bisphosphonate (eg, pamidronate or zoledronate) if expected survival is 3 months or longer and creatinine levels are below 3.0 mg/dL (Category 1).[100,101,102,103,104,105] Bisphosphonates may be given in addition to chemotherapy or hormonal therapy.

Women considered to be appropriate candidates for initial hormonal 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, nonsteroidal aromatase inhibitor such as anastrozole or letrozole as the preferred first-line therapy for their recurrent disease.[106,107] For postmenopausal women who are antiestrogen naïve or who are more than 1 year from previous antiestrogen therapy, the selective, nonsteroidal aromatase inhibitors appear to have superior outcome compared with tamoxifen, although the differences are modest.[108,109,110,111] 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 LRHR agonist is preferred.[112]

Many premenopausal and postmenopausal women with hormone-responsive breast cancer benefit from sequential hormonal therapy at the time of progression. Therefore, women whose breast cancers respond to a hormonal maneuver with either shrinkage of the tumor or long-term disease stabilization should receive additional hormonal therapy at the time of progression. Additional hormonal therapies for second-line and subsequent therapy are listed on in the algorithm (BINV-F). 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,[113,114] and a recent reanalysis of these studies suggests a longer duration of response favoring fulvestrant.[115] Hormonal 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 first or 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 wide variety of chemotherapy regimens are felt to be appropriate, as outlined in the treatment algorithm (BINV-G). 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 the anthracyclines, the taxanes, capecitabine, and vinorelbine. 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); and docetaxel, capecitabine. Other active agents include gemcitabine, platinum compounds, etoposide, vinblastine, and fluorouracil by continuous infusion. As with hormonal therapy, sequential responses are often observed with chemotherapy, supporting the use of sequential single agents and combination chemotherapy regimens.

Patients with tumors that overexpress HER2/*neu* may derive benefit from treatment with trastuzumab as a single agent or in combination with selected chemotherapeutic agents. The optimal method of selecting the subset of patients most likely to benefit from trastuzumab is rapidly evolving. When tested 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 IHC 3+ for HER2/*neu* by the HercepTest or IHC 2+ for HER2/*neu* by the HercepTest and FISH amplified.[116,117,118] Patients with tumors IHC 0 or 1+ for HER2/*neu* 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.[16,17]

In patients with metastatic or recurrent breast cancer whose tumors overexpress HER2/*neu*, trastuzumab as a single agent[25,27] or in combination with selected chemotherapeutics[26] 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.[26,119]

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 were based largely on the results of past and present clinical trials. However, there is not a single clinical situation in which the treatment of breast cancer has been optimized with respect to either maximizing cure or minimizing toxicity and disfigurement. Therefore, patient/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, Thomas A, Murray T, Thun M. Cancer statistics, 2002 CA Cancer J Clin 52:23-47, 2002.

2. Greene FL, Page DL, Fleming ID et al. AJCC Cancer Staging Manual, Sixth Edition. New York, NY, 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 20:3628-3636, 2002.

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

5. 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 16:1133-1143, 1992.

6. Haagensen CD, Bodian C, Haagensen DE. Breast carcinoma: Risk and detection. Philadelphia, PA: WB Saunders, 1981.

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

8. Fisher B, Costantino JP, Wickerham DL et al. moxifen for the prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 90:1371-1388, 1998b.

9. 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 16:441-452, 1998c.

10. 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 355:528-533, 2000.

11. Silverstein MJ, Lagios MD, Craig PH et al. A prognostic index for ductal carcinoma in situ. Cancer 77:2267-2274, 1996.

12. Silverstein MJ, Lagios MD, Groshen S et al. The influence of margin width on local control of ductal carcinoma in situ of the breast [see comments] N Engl J Med 340:1455-1461, 1999.

13. 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 Res Treat 69:210 (abstract 7), 2001.

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

15. 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 353:1993-2000, 1999.

16. 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 94:855-7, 2002.

17. 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 94:852-4, 2002.

18. 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 20:3095-3105, 2002.

19. 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 18:3651-3664, 2000.

20. Cooke TJ, Reeves J, Lanigan A et al. HER2 as a prognostic and predictive marker for breast cancer. Ann Oncol 12(suppl 1): S23-28, 2001.

21. 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 90:1361-1370, 1998.

22. 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 92:1991-1998, 2000.

23. 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 36:1755-1761, 2000.

24. Thor AD, Berry DA, Budman DR. ErbB-2, p53, and efficacy of adjuvant therapy in lymph node-positive breast cancer. J Natl Cancer Inst 90:1346-1360, 1998.

25. 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 17:2639-2648, 1999.

26. 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 344:783-792, 2001.

27. 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 37(suppl 1):25-29, 2001.

28. 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 33:278-282, 2001.

29. 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 19:354-363, 2001.

30. 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 19:2714-2721, 2001.

31. 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 53:374-381, 2000.

32. 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 14:1558-1564, 1996.

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

34. 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 347:1233-1241, 2002.

35. Veronesi U, Cascinelli N, Mariani L et al. Tweny-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 347:1227-1232, 2002.

36. Recht A, Come SE, Henderson IC et al. The sequencing of chemotherapy and radiation therapy after conservative surgery for early-stage breast cancer [see comments]. N Engl J Med 334:1356-61, 1996.

37. 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 21:331-338, 1991.

38. 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 45:877-884, 1999.

39. 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 35:661-668, 1996.

40. 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 28A:1415-8, 1992

41. Kiricuta CI, Tausch J. A mathematical model of axillary lymph node involvement based on 1446 complete axillary dissections in patients with breast carcinoma. Cancer 69:2496-501, 1992

42. Bass SS, Lyman GH, McCann CR et al. Lymphatic mapping and sentinel lymph node biopsy. Breast 5:288-295, 1999.

43. Cox CE. Lymphatic mapping in breast cancer: Combination technique. Ann Surg Oncol 8:67S-70S, 2001.

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

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

46. 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 339:990-995, 1998.

47. 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 186:423-427, 1998.

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

49. Dupont EC, Cox C, Shivers S et al. Learning curves and breast cancer lymphatic mapping: Institutional volume index. J Surg Res 97:92-96, 2001.

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

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

52. 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 337:949-955, 1997.

53. 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 353:1641-1648, 1999.

54. Ragaz JS, Jackson M, Le N et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 337:956-862, 1997.

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

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

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

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

59. 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 19:980-991, 2001.

60. 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 18:3471-3479, 2000.

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

62. 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 19:3376-3384, 2001.

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

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

65. 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 36:1755-1761, 2000.

66. ATAC Trialists' Group. 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 359:2131-9, 2002.

67. Duffy SR, Jackson TL, 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 21:40a (abstract 158), 2002.

68. Fallowfield L, 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 21:40a (abstract 158), 2002.

69. ATAC Trialists' Group. 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 85:317-24, 2001.

70. Ravdin P. Aromatase inhibitors for the endocrine adjuvant treatment of breast cancer. Lancet 359:2126-7, 2002.

71. Winer EP, Hudis C, Burstein HJ et al. American Society of Clinical Oncology Technology Assessment on the Use of Aromatase Inhibitors as Adjuvant Therapy for Women With Hormone Receptor--Positive Breast Cancer: Status Report 2002. J Clin Oncol 20:3313-3327, 2002.

72. Swain SM, Wilson J, Mamounas E et al. Estrogen receptor (ER) status of primary breast cancer is predictive of ER status of contralateral breast cancer (CBC). Proc Am Soc Clin Oncol 21:38a (abstract 150), 2002.

73. Wysowski DK, Honig SF, Beitz J. Uterine sarcoma associated with tamoxifen use. N Engl J Med 346:1832-3, 2002.

74. Albain KS, Green SJ, Ravdin PM 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 21:37a (abstract 143), 2002.

75. 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 330:1253-1259, 1994.

76. 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 19:329-335, 2001.

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

78. Pritchard KI, O'Malley FA, 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 21:(abstract 165), 2002.

79. 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 89:2521-2526, 2000

80. 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 19: 9310942, 2001.

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

82. Fisher B, Anderson D, Wickerham L 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 15:1858-1869, 1997.

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

84. 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 273:542-547, 1995.

85. 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 87:405-411, 2000.

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

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

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

89. 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. Proceedings of ASCO: 21(abstract 141), 2002

90. 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 18:2718-2727, 2000.

91. Early Breast Cancer Trialists' Group. Ovarian ablation in early breast cancer: Overview of randomised trials. Lancet 348: 1189-1196, 1996.

92. 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. In press, J Clin Oncol, 2002.

93. Hotobagyi GN, Singletary SE, Strom EA. Treatment of locally advanced and inflammatory breast cancer. In: Harris JR, ed: Diseases of the Breast. Philadelphia, Pa: Lippincott Williams and Wilkins, 2000.

94. Favret AM, Carlson RW, Goffinet DR et al. Locally advanced breast cancer: Is surgery necessary? Breast J 7:131-137, 2001.

95. Rosselli Del Turco M, Palli D, Cariddi A et al. Intensive diagnostic follow-up after treatment of primary breast cancer. JAMA 271:1593-1597, 1994.

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

97. The GIVO Investigators. Impact of follow-up testing on survival and health-related quality of life in breast cancer. JAMA 271:1587-1592, 1994.

98. 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 19:1865-1878, 2001

99. Wahl RL. Current status of PET in breast cancer imaging, staging, and therapy. Semin Roentgenol 36:250-60, 2001.

100. 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 14:2552-2559, 1996.

101. 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 16:2038-2044, 1998.

102. 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 17:846-854, 1999.

103. Berenson JR, Rosen LS, Howell A et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. Cancer 91:1191-200., 2001.

104. Ali SM, Esteva FJ, Hortobagyi G et al. Safety and efficacy of bisphosphonates beyond 24 months in cancer patients. J Clin Oncol 19:3434-7, 2001.

105. Hillner BE, Ingle JN, Berenson JR et al. American Society of Clinical Oncology Guideline on the Role of Bisphosphonates in Breast Cancer. J Clin Oncol 18:1378-1391, 2000.

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

107. 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 83:1142-1152, 1998.

108. 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 18:3748-3757, 2000.

109. 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 on the International Letrozole Breast Cancer Group J Clin Oncol 19:2596-2606, 2001.

110. 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 18: 3758-3767, 2000.

111. 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 36(suppl 4):S84-85, 2000.

112. 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 19:343-353, 2001.

113. 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 20:3386-3395, 2002.

114. Howell A, Robertson JFR, Albano JQ 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 20:3396-3403, 2002.

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

116. 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 33:278-282, 2001.

117. 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 19:2714-2721, 2001.

118. 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 53:374-381, 2000.

119. Seidman A, Hudis C, Pierri MK et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 20:1215-21, 2002.