National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Breast Cancer

V.1.2009

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[NCCN Guidelines Panel Disclosures]

Continue

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¶ Surgical Oncology
≠ Pathology
Ÿ Reconstructive Surgery
§ Radiation Oncology
ξ Bone Marrow Transplantation
¥ Patient Advocacy
* Writing Committee Member

Breast Cancer

Table of Contents

For help using these documents, please click here

Guidelines Index

Print the Breast Cancer Guideline

Staging

Manuscript

References

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

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

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

See NCCN Categories of Evidence and Consensus

Breast Cancer Update Summary

Guidelines Index
Breast Cancer TOC
Staging, Discussion, References

Summary of changes in the 1.2009 version of the NCCN Breast Cancer Guidelines from the 2.2008 version include:

DCIS-1
- Under the work-up section, added recommendation for genetic counseling if the patient is high risk for hereditary breast cancer.
- Footnote h added: "Post-excision mammography should also be performed whenever uncertainty about adequacy of excision remains."

BINV-1
- Under the work-up section, added recommendation for genetic counseling if the patient is high risk for hereditary breast cancer.
- Footnote d is new to the page: "The use of PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer."

BINV-2
- Changed recommendation for radiation therapy to whole breast with "or without" boost following lumpectomy.

BINV-5
- Added ± trastuzumab as a category 3 recommendation for systemic adjuvant treatment for tumors 0.6-1.0 cm, moderate/poorly differentiated or unfavorable features. Also added to BINV-7.
- Footnote u is new to the page: "The prognosis of patients with T1a and T1b tumors that are node negative is generally favorable even when HER2 is amplified or over-expressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy." Also added to BINV-7.

BINV-9
- Added repeat determination of tumor estrogen/progesterone receptor (ER/PR) status following ER/PR negative.

BINV-10
- Footnote d is new to the page: "The use of PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer."

BINV-12
- Added "Complete up to one year of trastuzumab therapy if HER2-positive (category 1). May be administered concurrent with radiation therapy and with endocrine therapy if indicated. If capecitabine administered as a radiation sensitizer, trastuzumab may be given concurrent with the capecitabine." under adjuvant treatment. Also added to BINV-14.

BINV-13
- Footnote z is new to the page: "The use of PET or PET/CT scanning should generally be discouraged for the evaluation of locally advanced disease except in those clinical situations where other staging studies are equivocal or suspicious. Even in these situations, biopsy of equivocal or suspicious sites is more likely to provide useful information. Also added to BINV-15

BINV-14
- Footnote w has been revised: "Patients with HER2 positive tumors should be treated with preoperative chemotherapy incorporating trastuzumab for at least 9 weeks of preoperative therapy."

BINV-15
- Added "...bone mineral density determination at baseline and periodically thereafter" to surveillance/follow-up.
- Footnote aa is new to the page: "The use of estrogen, progesterone, or selective estrogen receptor modulators to treat osteoporosis or osteopenia in women with breast cancer is discouraged. The use of a bisphosphonate is generally the preferred intervention to improve bone mineral density. Current clinical trials support the use of bisphosphonate for up to 2 years. Longer duration of bisphosphonate therapy may provide additional benefit, but this has not yet been tested in clinical trials. Women treated with a bisphosphonate should undergo a dental examination with preventive dentistry prior to the initiation of therapy, and should take supplemental calcium (1200-1500 mg/day) and vitamin D (400-800 IU/day)."

BINV-16
- Added a new pathway for local recurrence with initial treatment mastectomy and no prior radiation therapy.

BINV-17
- Footnote ff is new to the page: "Women presenting at time of initial diagnosis with metastatic disease may benefit from the performance of local breast surgery and/'or radiation therapy. Generally this palliative local therapy should be considered only after response to initial systemic therapy."

BINV-18
- Footnote hh is new to the page: False negative ER and/or PR determinations occur, and there may be discordance between the ER and/or the PR determination between the primary and metastatic tumor(s). Therefor, endocrine therapy with its low attendant toxicity may be considered in patients with non-visceral or asymptomatic visceral tumors. especially in patients with clinical characteristics predicting for a hormone receptor positive tumor (eg, long disease free interval, limited sites of recurrence, indolent disease, or older age). Also added to BINV-19.

BINV-B
- Principles of Dedicated Breast MRI Testing - this page has been updated and includes 6 new bulleted recommendations.

BINV-G
- New title "Principles of Breast Reconstruction Following Surgery" includes 2 new recommendations for cosmetic outcome before and after surgery.

BINV-J and BINV-M
- Chemotherapy pages were reorganized, dose schedules provided and references updated.

PREG-1
- Footnote c has been revised: "There are insufficient data to recommend general use of sentinel node procedures, a taxane or trastuzumab during pregnancy.

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Lobular Carcinoma in Situ

DIAGNOSIS	WORKUP	PRIMARY TREATMENT	RISK REDUCTION	SURVEILLANCE/FOLLOW-UP
Lobular carcinoma in situ (LCIS) Stage 0 Tis, N0, M0[a]	• History and physical • Diagnostic bilateral mammogram • Pathology review[b]	Observation[c]	Counseling regarding risk reduction with tamoxifen for premenopausal women,[d] or with tamoxifen or raloxifene for postmenopausal women (category 1, see also NCCN Breast Cancer Risk Reduction Guidelines) or In special circumstances, bilateral mastectomy (see also NCCN Breast Cancer Risk Reduction Guidelines) ± reconstruction[e] may be considered for risk reduction	• Interval history and physical exam every 6-12 mo • Mammogram every 12 mo, unless postbilateral mastectomy • If treated with tamoxifen, monitor per NCCN Breast Cancer Risk Reduction Guidelines

[a] See NCCN Breast Cancer Screening and Diagnosis Guidelines.

[b] The panel endorses the College of American Pathology Protocol for pathology reporting for all invasive and non-invasive carcinomas of the breast. http://www.cap.org

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

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

[e] See Principles of Breast Reconstruction Following Surgery (BINV-G).

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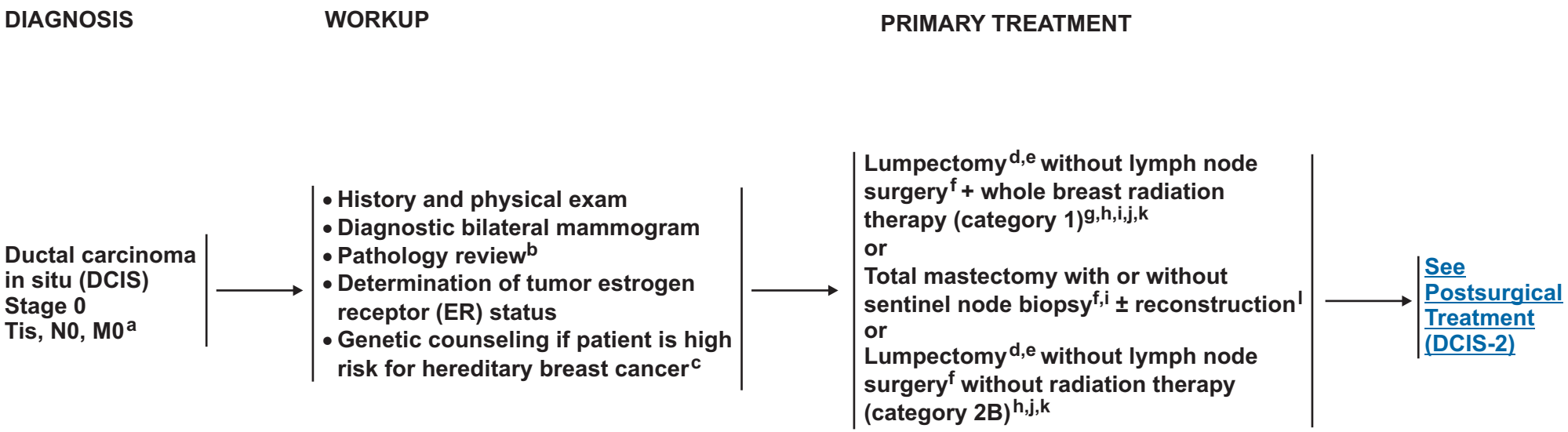
Ductal Carcinoma in Situ



[a] See NCCN Breast Cancer Screening and Diagnosis Guidelines.

[b] The panel endorses the College of American Pathology Protocol for pathology reporting for all invasive and non-invasive carcinomas of the breast. http://www.cap.org

[c] See NCCN Genetic/Familial High-Risk Assessment.

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

[e] See Margin Status in DCIS (DCIS-A).

[f] 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.

[g] See Principles of Radiation Therapy (BINV-H).

[h] Complete resection should be documented by analysis of margins and specimen radiography. Post-excision mammography should also be performed whenever uncertainty about adequacy of excision remains.

[i] 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.

[j] See Special Considerations Breast-Conserving Therapy (BINV-F).

[k] Whole breast radiation therapy following lumpectomy reduces recurrence rates in DCIS by about 50%. Approximately half of the recurrences are invasive and half DCIS. A number of factors determine that local recurrence risk, include size, tumor grade, margin status and patient age. Some patients may be treated by excision alone, if the patient and physician view the individual risks as "low". All data evaluating the three local treatments show no differences in patient survival.

[l] See Principles of Breast Reconstruction Following Surgery (BINV-G).

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Ductal Carcinoma in Situ

DCIS POSTSURGICAL TREATMENT

Risk reduction therapy for ipsilateral breast following breast conserving surgery:
Consider tamoxifen[m] for 5 years for:

- **Patients treated with breast-conserving therapy (lumpectomy) and radiation therapy (category 1),[n] especially for those with ER-positive DCIS. The benefit of tamoxifen for ER-negative DCIS is uncertain**
- **Patients treated with excision alone[n]**

Risk reduction therapy for contralateral breast:

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

→

SURVEILLANCE/FOLLOW-UP

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

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

[n] Available data suggest tamoxifen provides risk reduction in the ipsilateral breast treated with breast conservation and in the contralateral breast in patients with mastectomy or breast conservation with ER-positive primary tumors. Since a survival advantage has not been demonstrated, individual consideration of risks and benefits is important (See also NCCN Breast Cancer Risk Reduction Guidelines).

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Ductal Carcinoma in Situ

MARGIN STATUS IN DCIS

Substantial controversy exists regarding the definition of a negative pathologic margin in DCIS. Controversy arises out of the heterogeneity of the disease, difficulties in distinguishing the spectrum of hyperplastic conditions, anatomic considerations of the location of the margin, and inadequate prospective data on prognostic factors in DCIS. Margins greater than 10 mm are widely accepted as negative (but may be excessive and may lead to a less optimal cosmetic outcome). Margins less than 1 mm are considered inadequate. With pathologic margins between 1-10 mm, wider margins are generally associated with lower local recurrence rates. However, close surgical margins (< 1 mm) at the fibroglandular boundary of the breast (chest wall or skin) do not mandate surgical re-excision but can be an indication for higher boost dose radiation to the involved lumpectomy site. (category 2B)

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Invasive Breast Cancer

CLINICAL STAGE

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

→

WORKUP

General workup including:
- **History and physical exam**
- **CBC, platelets**
- **Liver function tests and alkaline phosphatase**
- **Diagnostic bilateral mammogram, ultrasound as necessary**
- **Pathology review[a]**
- **Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER2 status[b]**

Optional additional studies for breast imaging:
- **Breast MRI[c]**

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

→ **See Locoregional Treatment (BINV-2)**

[a] The panel endorses the College of American Pathology Protocol for pathology reporting for all invasive and non-invasive carcinomas of the breast. http://www.cap.org.
[b] See Principles of HER2 Testing (BINV-A).
[c] See Principles of Dedicated Breast MRI Testing (BINV-B).
[d] The use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer.
[e] See NCCN Genetics/Familial High-Risk Assessment.

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Invasive Breast Cancer

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

Lumpectomy with surgical axillary staging (category 1)[f,g,h]

or

- **≥ 4 positive axillary nodes[k]** → **Radiation therapy to whole breast with or without boost[k] (by photons, brachytherapy, or electron beam) to tumor bed and supraclavicular area (category 1). Consider radiation therapy to internal mammary nodes[l] (category 3), radiation therapy may be given concurrent with CMF (category 2B) or follow chemotherapy when chemotherapy indicated.**
- **1-3 positive axillary nodes** → **Radiation therapy to whole breast with or without boost[k] (by photons, brachytherapy, or electron beam) to tumor bed (category 1). Consider radiation therapy to supraclavicular area (category 2B). Consider radiation therapy to internal mammary nodes[l] (category 3). Radiation therapy may be given concurrent with CMF (category 2B) or follow chemotherapy when chemotherapy indicated.**
- **Negative axillary nodes** → **Radiation therapy to whole breast with or without boost[k] (by photons, brachytherapy, or electron beam) to tumor bed.[m] Radiation therapy may be given concurrent with CMF (category 2B) or follow chemotherapy when chemotherapy indicated.**

→ See BINV-4

Total mastectomy with surgical axillary staging[f,g] (category 1) ± reconstruction[i] → See Locoregional Treatment (BINV-3)

or

If T2 or T3 and fulfills criteria for breast conserving therapy except for size[h] → Consider Preoperative Chemotherapy Guideline (BINV-10)

[f] See Surgical Axillary Staging (BINV-C).
[g] See Axillary Lymph Node Staging (BINV-D) and Margin Status in Infiltrating Carcinoma (BINV-E).
[h] See Special Considerations to Breast-Conserving Therapy (BINV-F).
[i] See Principles of Reconstruction Following Surgery (BINV-G).
[j] Consideration may be given to additional staging including bone scan and abdominal CT/US/MRI; chest CT (category 2B).
[k] See Principles of Radiation Therapy (BINV-H).
[l] Radiation therapy should be given to the internal mammary lymph nodes if they are clinically or pathologically positive, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be utilized in all cases where radiation therapy is delivered to the internal mammary lymph nodes.
[m] Breast irradiation may be omitted in those 70 y of age or older with estrogen-receptor positive, clinically node negative, T1 tumors who receive adjuvant endocrine therapy (category 1).

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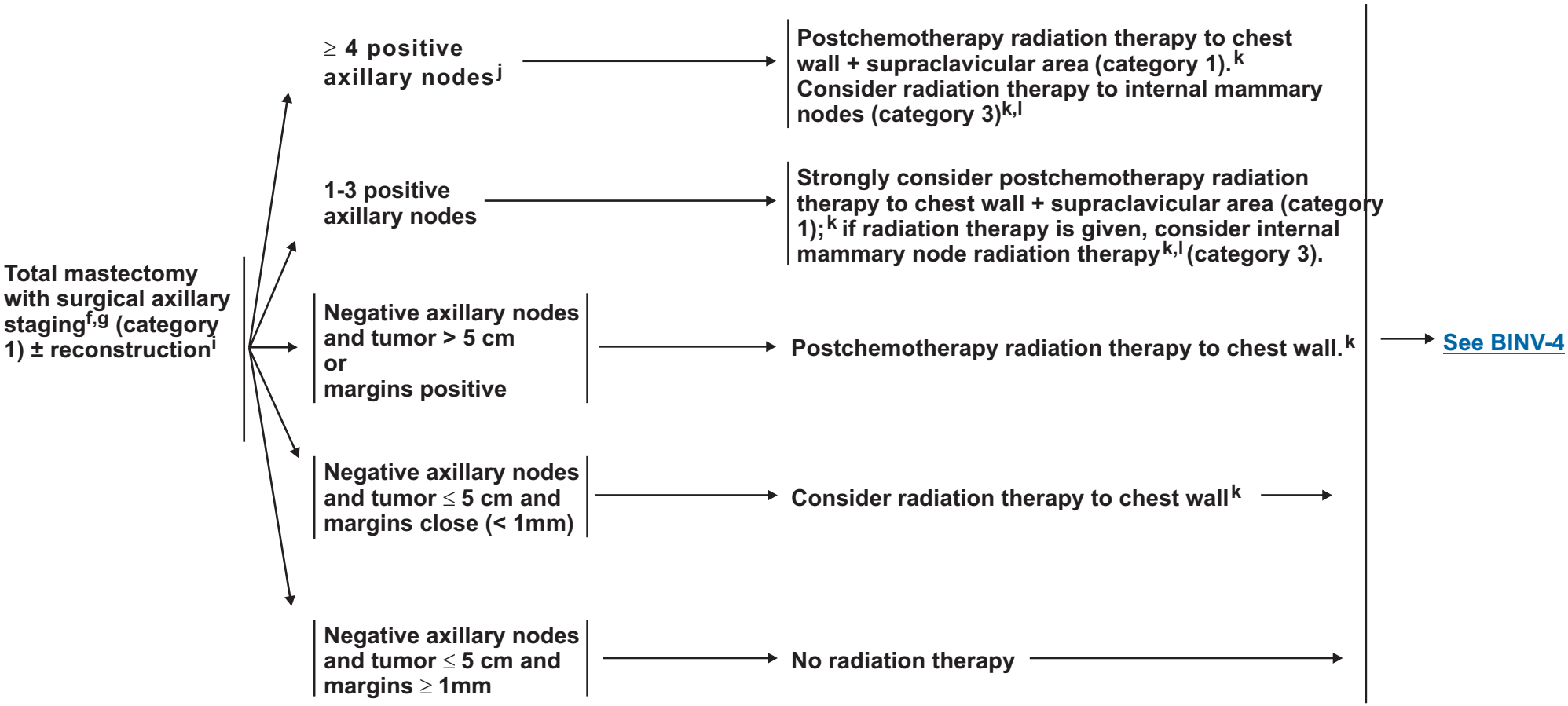
LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3, N1, M0



[f] See Surgical Axillary Staging (BINV-C).
[g] See Axillary Lymph Node Staging (BINV-D) and Margin Status in Infiltrating Carcinoma (BINV-E).
[i] See Principles of Reconstruction Following Surgery (BINV-G).
[j] Consideration may be given to additional staging including bone scan; abdominal CT/US/MRI; chest CT (category 2B).
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[l] Radiation therapy should be given to the internal mammary lymph nodes that are clinically or pathologically positive, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be utilized in all cases where radiation therapy is delivered to the internal mammary lymph nodes.

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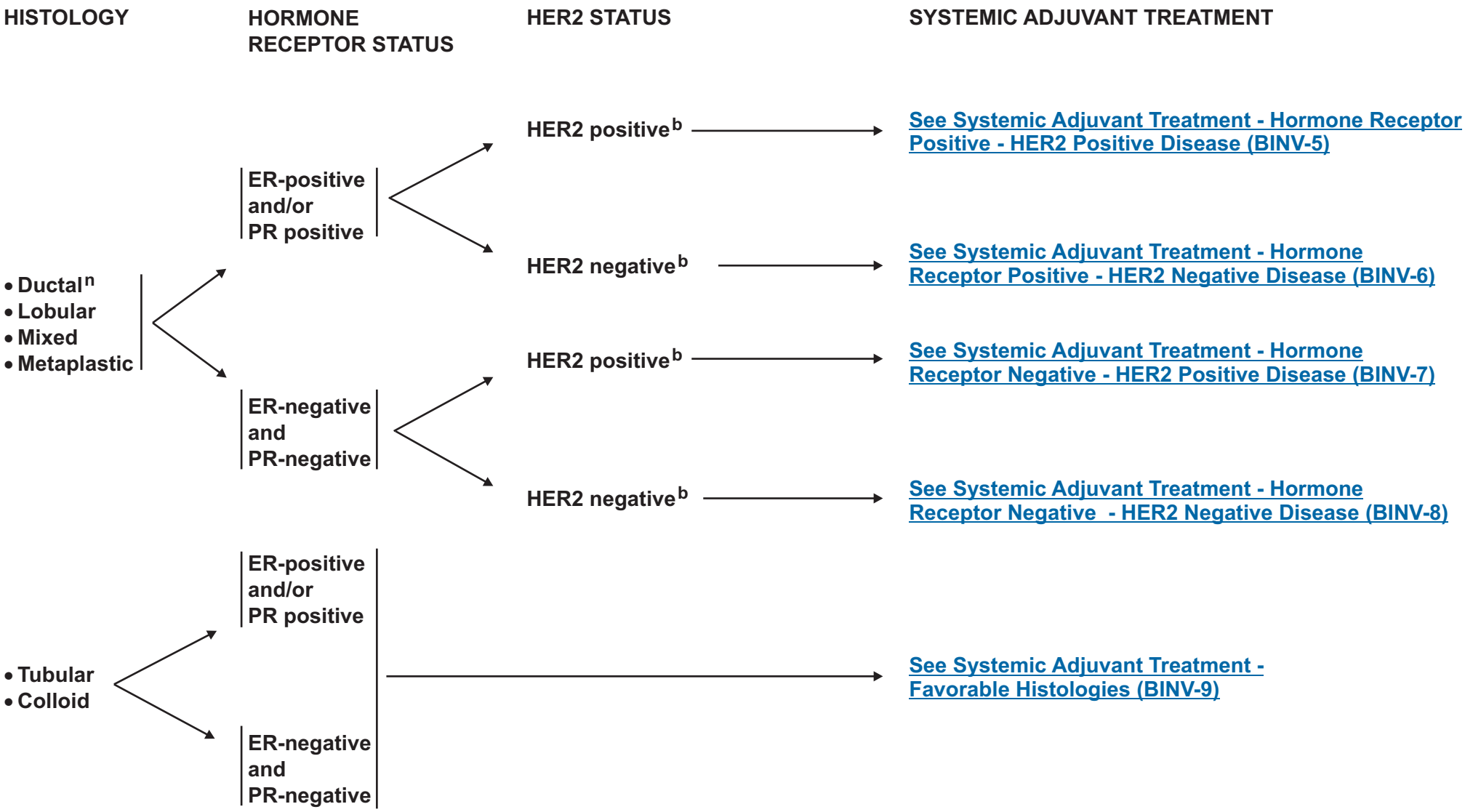

[b] See Principles of HER2 Testing (BINV-A).

[n] This includes medullary and micropapillary subtypes.

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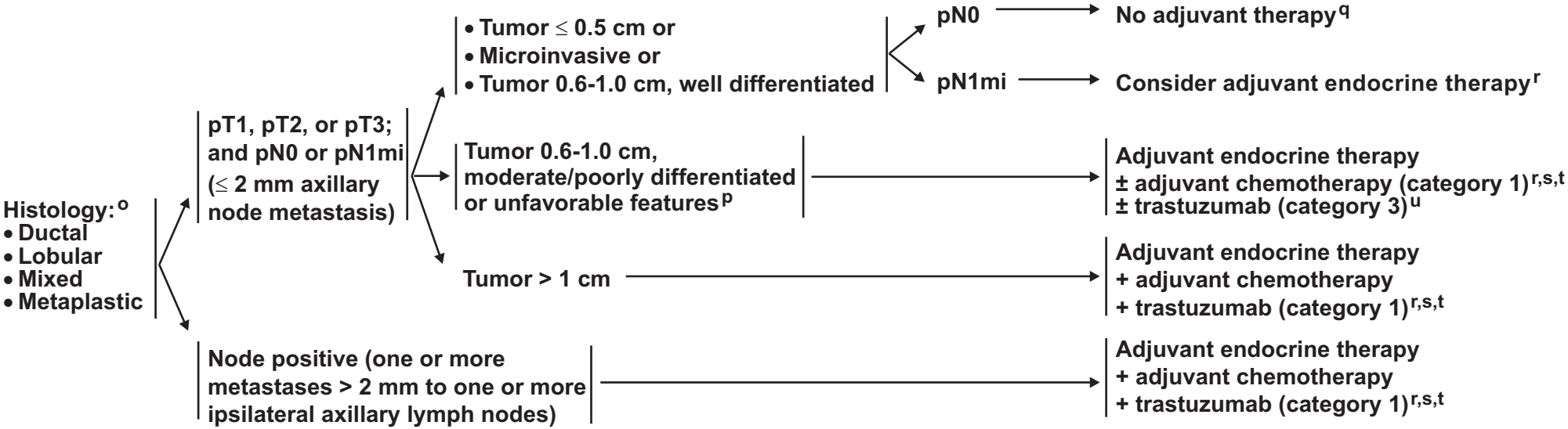
SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR POSITIVE - HER2 POSITIVE DISEASE[b]



See Follow-Up (BINV-15)
See Adjuvant Endocrine Therapy (BINV-I) and Adjuvant Chemotherapy (BINV-J)

[b] See Principles of HER2 Testing (BINV-A).

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

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

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

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

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

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

[u] The prognosis of patients with T1a and T1b tumors that are node negative is generally favorable even when HER2 is amplified or over-expressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.

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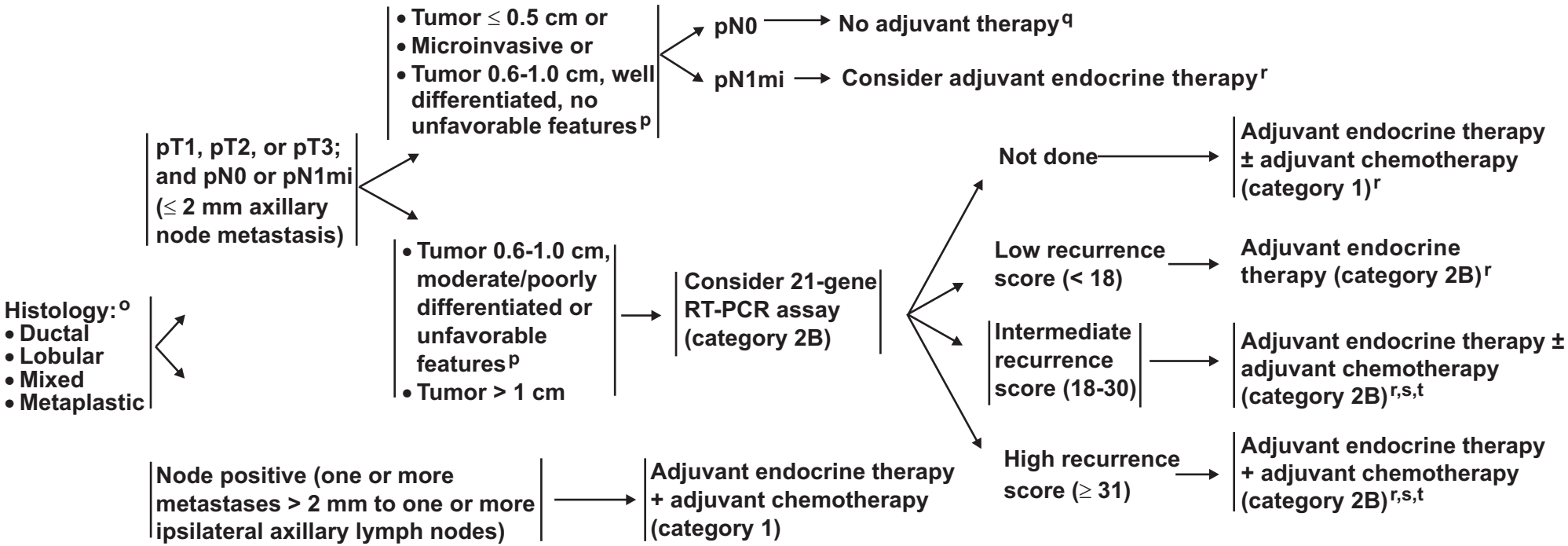

See Adjuvant Endocrine Therapy (BINV-I) and Adjuvant Chemotherapy (BINV-J)

[b] See Principles of HER2 Testing (BINV-A).

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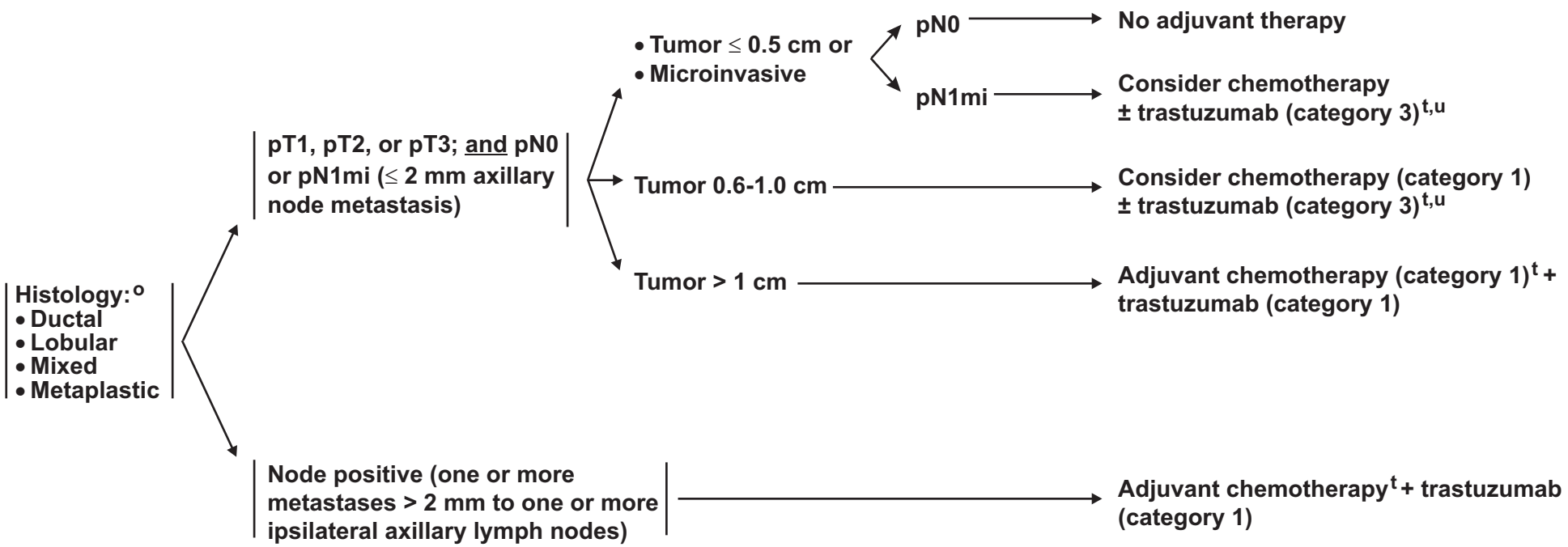

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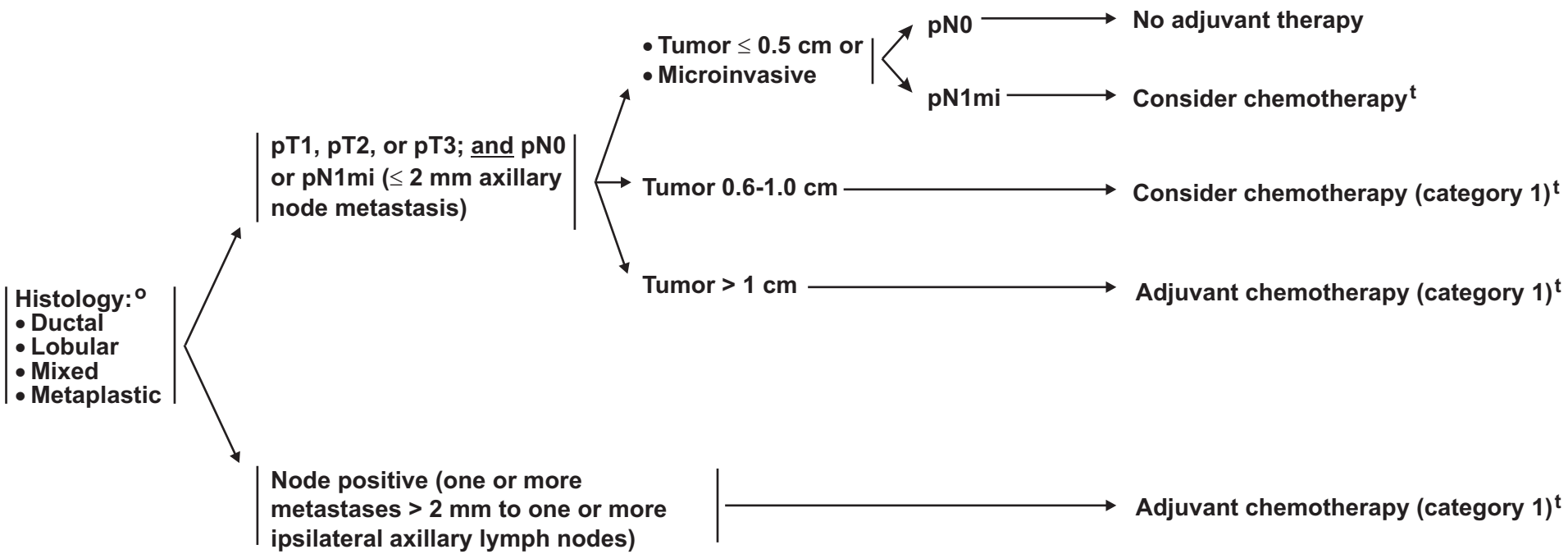

See Follow-Up (BINV-15)
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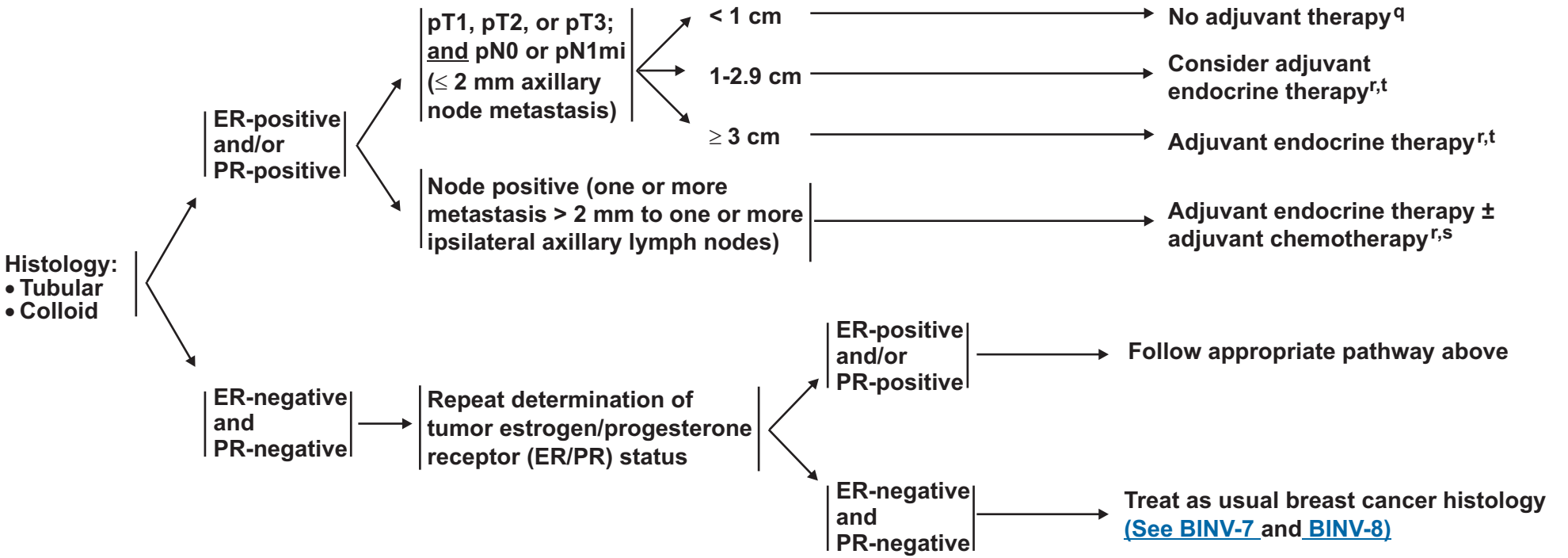
SYSTEMIC ADJUVANT TREATMENT - FAVORABLE HISTOLOGIES



See Adjuvant Endocrine Therapy (BINV-I) and Adjuvant Chemotherapy (BINV-J)

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

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

Preoperative Chemotherapy Guideline

CLINICAL STAGE

Stage IIA
T2, N0, M0

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

Stage IIIA
T3, N1, M0

and

Fulfills criteria for breast conserving surgery except for tumor size

→

WORKUP

General workup including:

- **History and physical**
- **CBC, platelets**
- **Liver function tests and alkaline phosphatase**
- **Diagnostic bilateral mammogram, ultrasound as necessary**
- **Pathology review[a]**
- **Determination of tumor ER/PR status and HER2 status[b]**

Additional studies or as indicated by symptoms:[d]

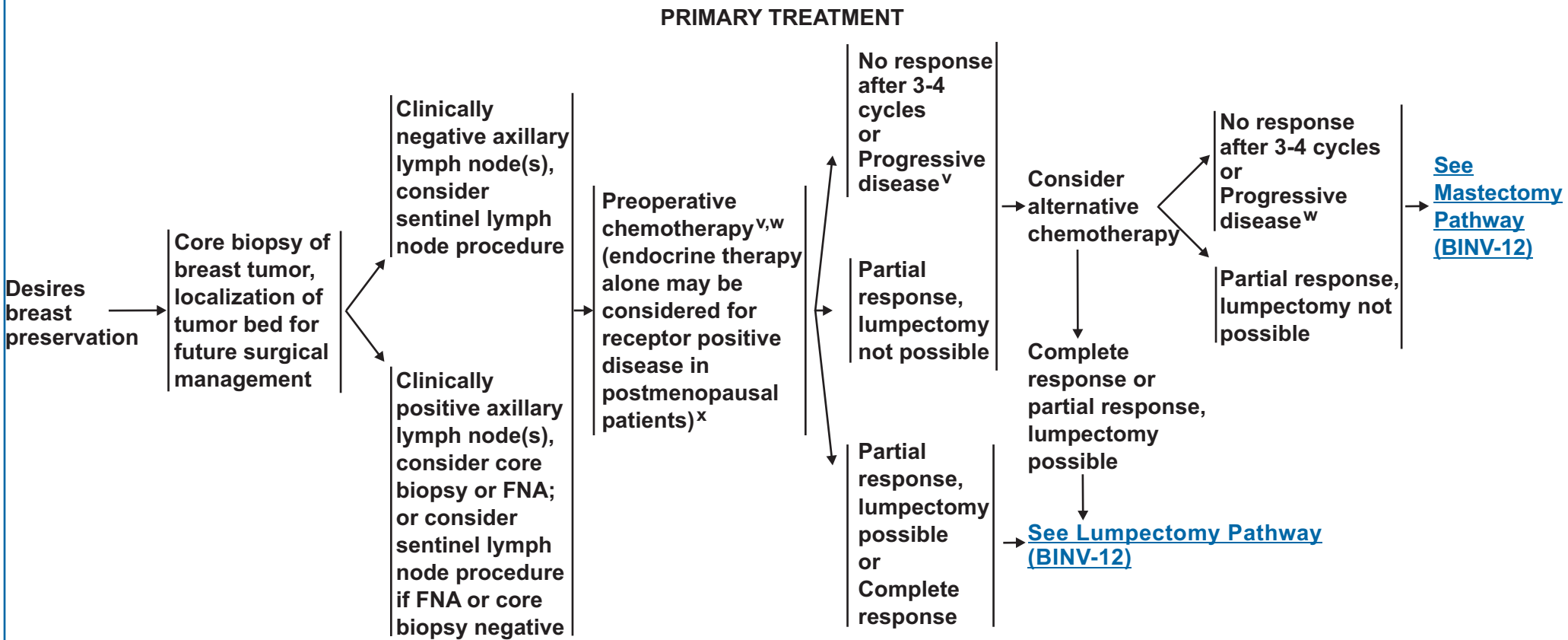
- **Breast MRI (optional)[c]**
- **Bone scan (optional) (indicated if localized symptoms or elevated alkaline phosphatase or if T3, N1, M0) (category 2B)**
- **Abdominal ± pelvis CT or US or MRI (optional for stage IIA or IIB, indicated if elevated alkaline phosphatase, abnormal LFTs, abdominal symptoms, abnormal physical examination of the abdomen, or if T3, N1, M0) (category 2B)**
- **Chest imaging (if pulmonary symptoms are present)**

→ **See Primary Treatment (BINV-11)**

[a] The panel endorses the College of American Pathology Protocol for pathology reporting for all invasive and non-invasive carcinomas of the breast. http://www.cap.org
[b] See Principles of HER2 Testing (BINV-A).
[c] See Principles of Dedicated Breast MRI Testing (BINV-B).
[d] The use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer.

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

Preoperative Chemotherapy Guideline



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

[d] See Surgical Axillary Staging (BINV-C).

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

[w] Patients with HER2-positive tumors should be treated with preoperative chemotherapy incorporating trastuzumab for at least 9 weeks of preoperative therapy (See BINV-J).

[x] Definition of Menopause (See BINV-K).

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

LOCAL TREATMENT

ADJUVANT TREATMENT

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

→ **Consider additional chemotherapy in the context of a clinical trial** →

- **Adjuvant radiation therapy post-mastectomy is based on prechemotherapy tumor characteristics as per BINV-3[k]**
  and
- **Endocrine therapy if ER-positive and/or PR-positive (category 1)[s]**
- **Complete up to one year of trastuzumab therapy if HER2-positive (category 1). May be administered concurrent with radiation therapy[k] and with endocrine therapy if indicated. If capecitabine administered as a radiation sensitizer, trastuzumab may be given concurrent with the capecitabine.**

See Adjuvant Endocrine Therapy (BINV-I)

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

→ **Consider additional chemotherapy in the context of a clinical trial** →

- **Adjuvant radiation therapy post-lumpectomy based on prechemotherapy tumor characteristics as per BINV-2[k]**
  and
- **Endocrine therapy if ER-positive and/or PR-positive (category 1)[s]**
- **Complete up to one year of trastuzumab therapy if HER2-positive (category 1). May be administered concurrent with radiation therapy[k] and with endocrine therapy if indicated. If capecitabine administered as a radiation sensitizer, trastuzumab may be given concurrent with the capecitabine.**

See Adjuvant Endocrine Therapy (BINV-I)

→ **See Surveillance/ Follow-up (BINV-15)**

[k] See Principles of Radiation Therapy (BINV-H).

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

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

Note: All recommendations are category 2A unless otherwise indicated.
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LOCALLY ADVANCED INVASIVE BREAST CANCER (NON-INFLAMMATORY)

CLINICAL STAGE

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

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

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

Stage IIIC
Any T, N3, M0

WORKUP

- History and physical exam
- CBC, platelets
- Liver function tests and alkaline phosphatase
- Chest imaging
- Diagnostic bilateral mammogram, ultrasound as necessary
- Pathology review
- Prechemotherapy determination of tumor ER/PR status and HER2 status[b]

Optional additional studies or as directed by symptoms or other abnormal staging studies:[z]

- Breast MRI[c]
- Bone scan (category 2B)
- Abdominal ± pelvic CT or US or MRI (category 2B)

→ See Preoperative Chemotherapy and Locoregional Treatment (BINV-14)

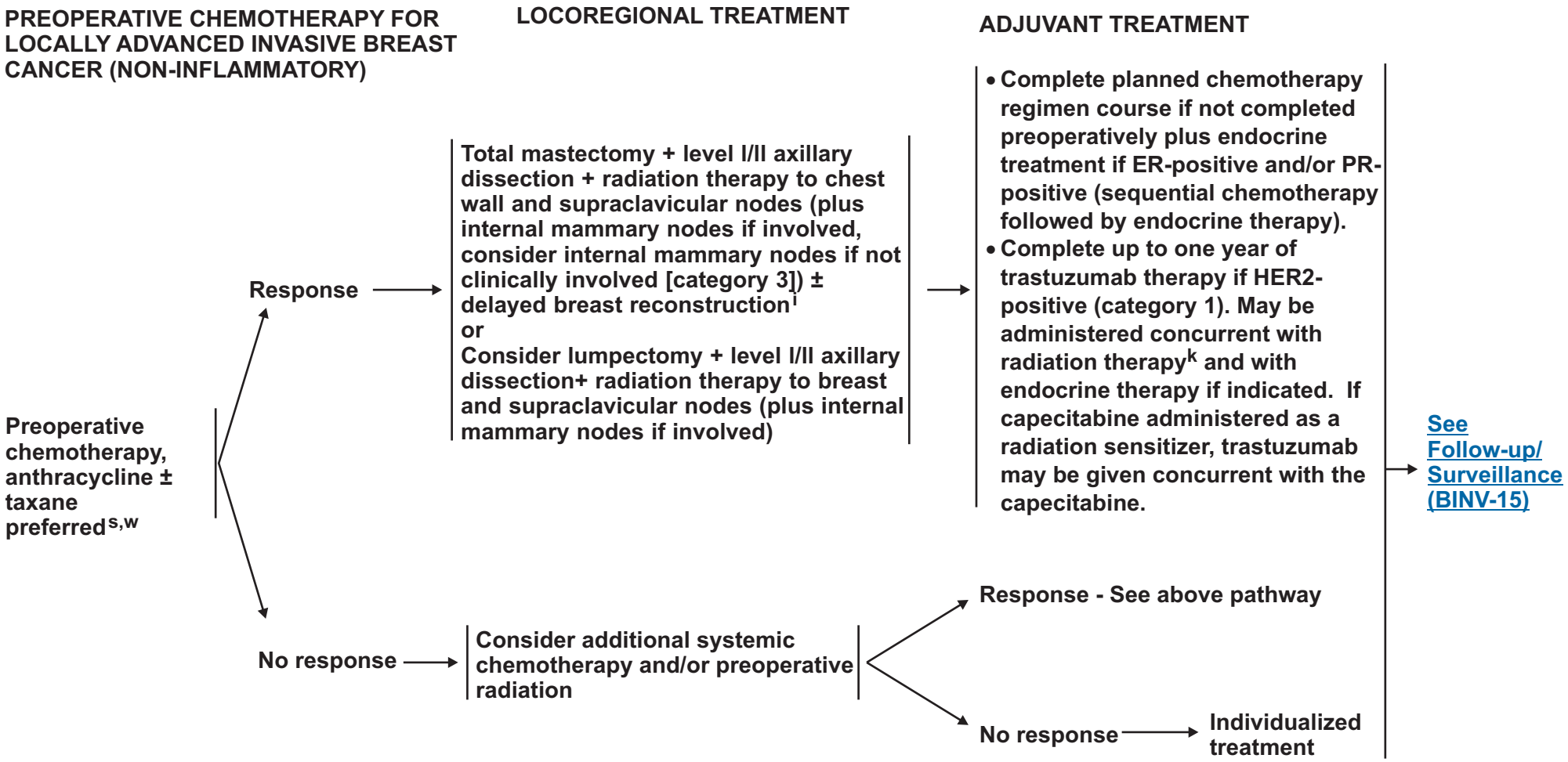
Stage IV
Any T, any N, M1

→ See Initial Workup for Stage IV Disease (BINV-15)

[b] See Principles of HER2 Testing (BINV-A).
[c] See Principles of Dedicated Breast MRI Testing (BINV-B).
[z] The use of PET or PET/CT scanning should generally be discouraged for the evaluation of locally advanced disease except in those clinical situations where other staging studies are equivocal or suspicious. Even in these situations, biopsy of equivocal or suspicious sites is more likely to provide useful information.

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



[k] See Principles of Radiation Therapy (BINV-H).

[i] See Principles of Reconstruction Following Surgery (BINV-G).

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

[w] Patients with HER2-positive tumors should be treated with preoperative chemotherapy incorporating trastuzumab for at least 9 weeks of preoperative therapy (See BINV-J).

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Invasive Breast Cancer

SURVEILLANCE/FOLLOW-UP

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

→

RECURRENT WORKUP or INITIAL WORKUP FOR STAGE IV DISEASE

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

→ Local disease only

→ Systemic disease

See Treatment of Recurrence/ Stage IV Disease (BINV-16)

[b] See Principles of HER2 Testing (BINV-A).

[aa] The use of estrogen, progesterone, or selective estrogen receptor modulators to treat osteoporosis or osteopenia in women with breast cancer is discouraged. The use of a bisphosphonate is generally the preferred intervention to improve bone mineral density. Current clinical trials support the use of bisphosphonate for up to 2 years. Longer duration of bisphosphonate therapy may provide additional benefit, but this has not yet been tested in clinical trials. Women treated with a bisphosphonate should undergo a dental examination with preventive dentistry prior to the initiation of therapy, and should take supplemental calcium (1200-1500 mg/day) and vitamin D (400-800 IU/day).

[bb] The use of PET or PET/CT scanning should generally be discouraged for the evaluation of metastatic disease except in those clinical situations where other staging studies are equivocal or suspicious. Even in these situations, biopsy of equivocal or suspicious sites is more likely to provide useful information.

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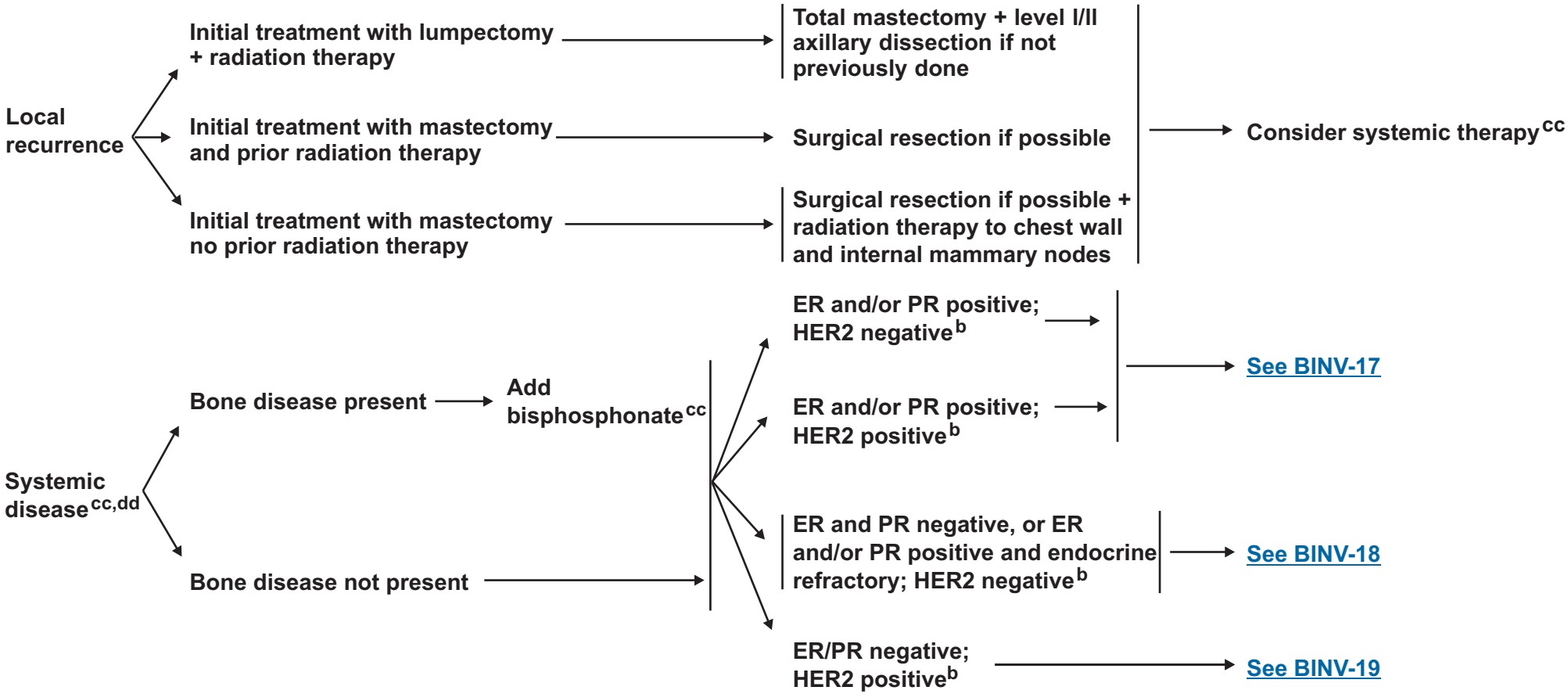
Invasive Breast Cancer

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE



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

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

[b] See Principles of HER2 Testing (BINV-A).

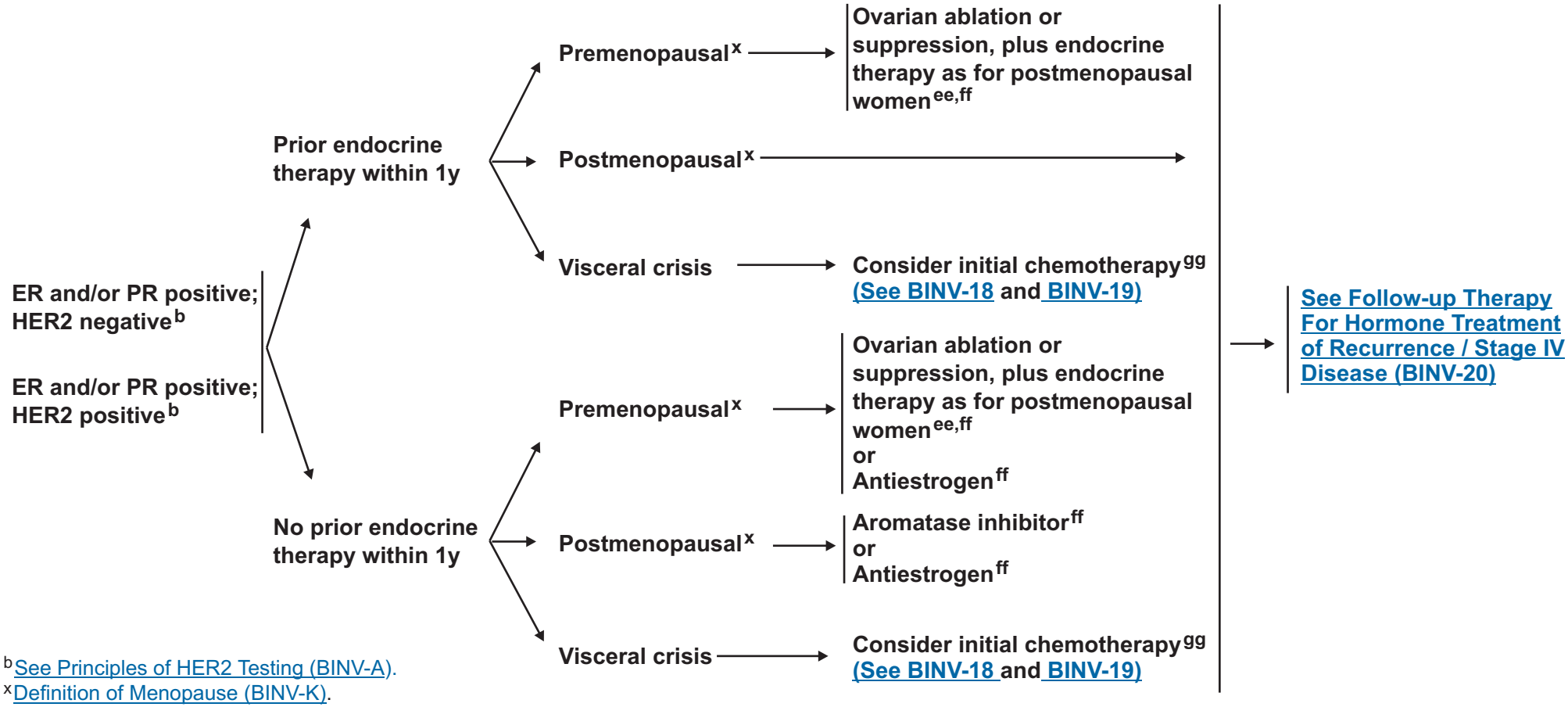
[cc] Pamidronate or zoledronic acid (with calcium 1200-1500 mg and vitamin D 400-800 IU daily supplement) should be given (category 1) in addition to chemotherapy or endocrine therapy if bone metastasis present, expected survival ≥ 3 months, and creatinine < 3.0 mg/dL. Patients should undergo a dental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

[dd] See NCCN Palliative Care Guidelines.

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

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE

ER and/or PR POSITIVE; HER2 NEGATIVE OR POSITIVE



[b] See Principles of HER2 Testing (BINV-A).
[x] Definition of Menopause (BINV-K).
[ee] See Subsequent Endocrine Therapy (BINV-L).
[ff] Women presenting at time of initial diagnosis with metastatic disease may benefit from the performance of local breast surgery and/or radiation therapy. Generally this palliative local therapy should be considered only after response to initial systemic therapy.
[gg] See Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-M).

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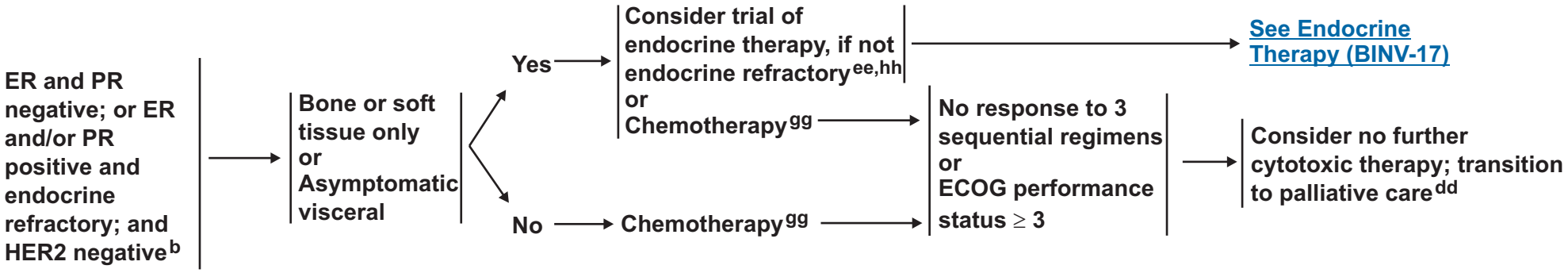
SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE

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

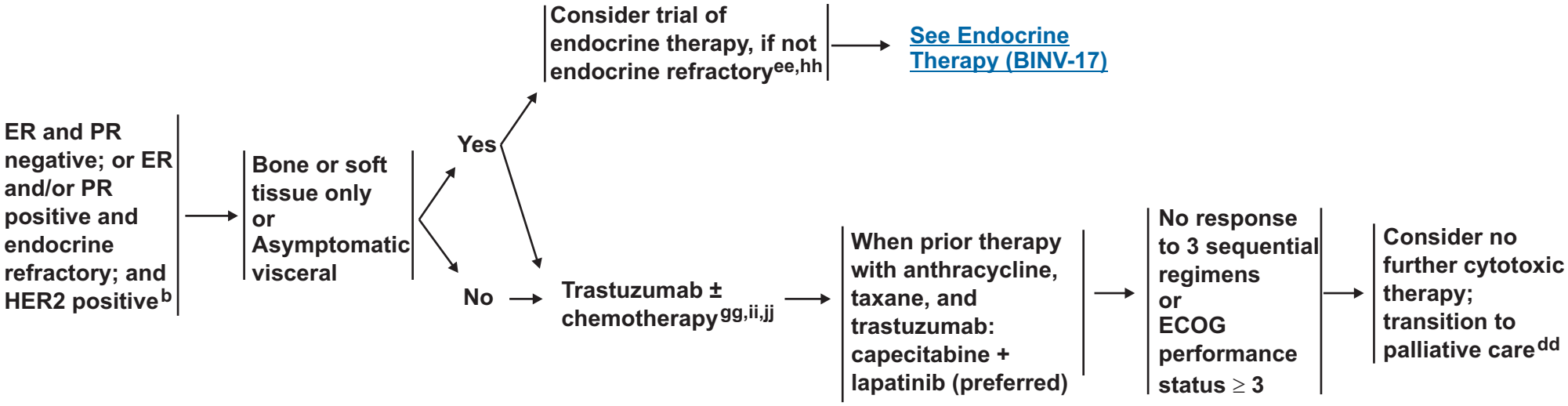


[b] See Principles of HER2 Testing (BINV-A).
[dd] See NCCN Palliative Care Guidelines.
[ee] See Subsequent Endocrine Therapy (BINV-L).
[gg] See Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-M).
[hh] False negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy with its low attendant toxicity may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a hormone receptor positive tumor (eg, long disease free interval, limited sites of recurrence, indolent disease, or older age).

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

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE

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



[b] See Principles of HER2 Testing (BINV-A).

[dd] See NCCN Palliative Care Guidelines.

[ee] See Subsequent Endocrine Therapy (BINV-L).

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

[hh] False negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy with its low attendant toxicity may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a hormone receptor positive tumor (eg, long disease free interval, limited sites of recurrence, indolent disease, or older age).

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

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

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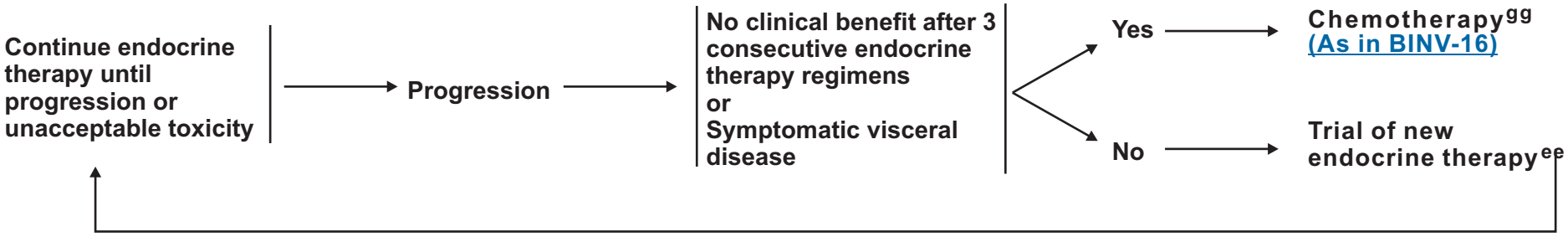
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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



[ee] See Subsequent Endocrine Therapy (BINV-L).
[gg] See Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-M).

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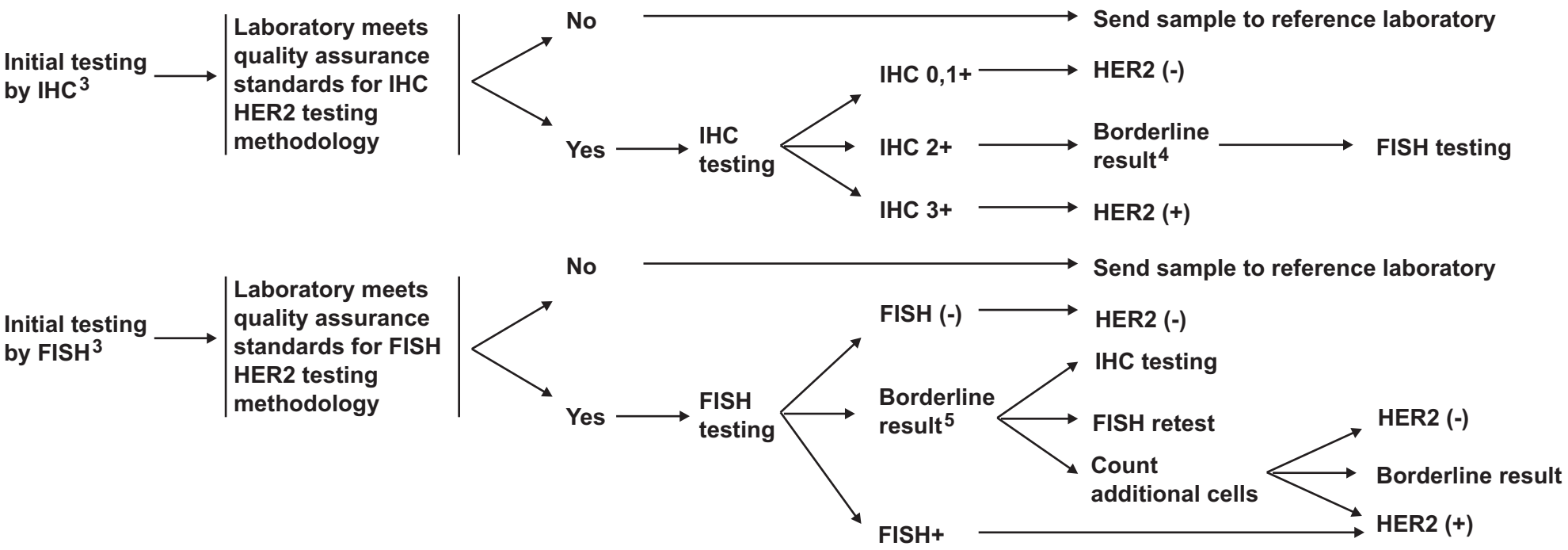
Invasive Breast Cancer

Guidelines Index
Breast Cancer TOC
Staging, Discussion, References

PRINCIPLES OF HER2 TESTING[1,2]



[1] See also, Carlson RW, Moench SJ, Hammond, MEH, et al. HER2 testing in breast cancer: NCCN task force report and recommendations. JNCCN 4:S-1-S-24, 2006.

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

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

[4] Borderline IHC samples (eg, IHC 2+) are subjected to reflex testing by a validated complementary (eg, FISH) method that has shown at least 95% concordance between IHC 0, 1+ results and FISH non-amplified results, and IHC 3+ results and FISH amplified results.

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

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PRINCIPLES OF DEDICATED BREAST MRI TESTING

See NCCN Breast Screening and Diagnosis Guidelines for indications for screening MRI in women at increased breast cancer risk.

Personnel, facility and equipment

- **Breast MRI examinations should be performed and interpreted by an expert breast imaging team working in concert with the multidisciplinary treatment team.**
- **Breast MRI examinations require a dedicated breast coil and breast imaging radiologists familiar with the optimal timing sequences and other technical details for image interpretation. The imaging center should have the ability to perform MRI guided needle sampling and/or wire localization of MRI detected findings.**

Clinical indications and applications

- **May be used for staging evaluation to define extent of cancer or presence of multifocal or multicentric cancer in the ipsilateral breast, or as screening of the contralateral breast cancer at time of initial diagnosis (category 2B). There are no data that demonstrate that use of MRI to affect choice of local therapy improves outcome (local recurrence or survival).**
- **May be helpful for breast cancer evaluation before and after neoadjuvant therapy to define extent of disease, response to treatment, and potential for breast conserving therapy.**
- **May be useful to detect additional disease in women with mammographically dense breast, but available data do not show differential detection rates by any subset by breast pattern (breast density) or disease type (eg. DCIS, invasive ductal cancer, invasive lobular cancer)**
- **May be useful for identifying primary cancer in women with axillary nodal adenocarcinoma or with Paget's disease of the nipple with breast primary not identified on mammography, ultrasound, or physical examination**
- **Falsely positive findings on breast MRI are common. Surgical decisions should not be based solely on the MRI findings. Additional tissue sampling of areas of concern identified by breast MRI is recommended.**
- **Utility in follow-up screening of ipsilateral and contralateral breast of women with prior breast cancer is not defined.**

Houssami N, Ciatto S, Macaskill P, Lord SJ, Warren RM, Dixon JM, Irwig L. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol 2008;26:3248-3258.

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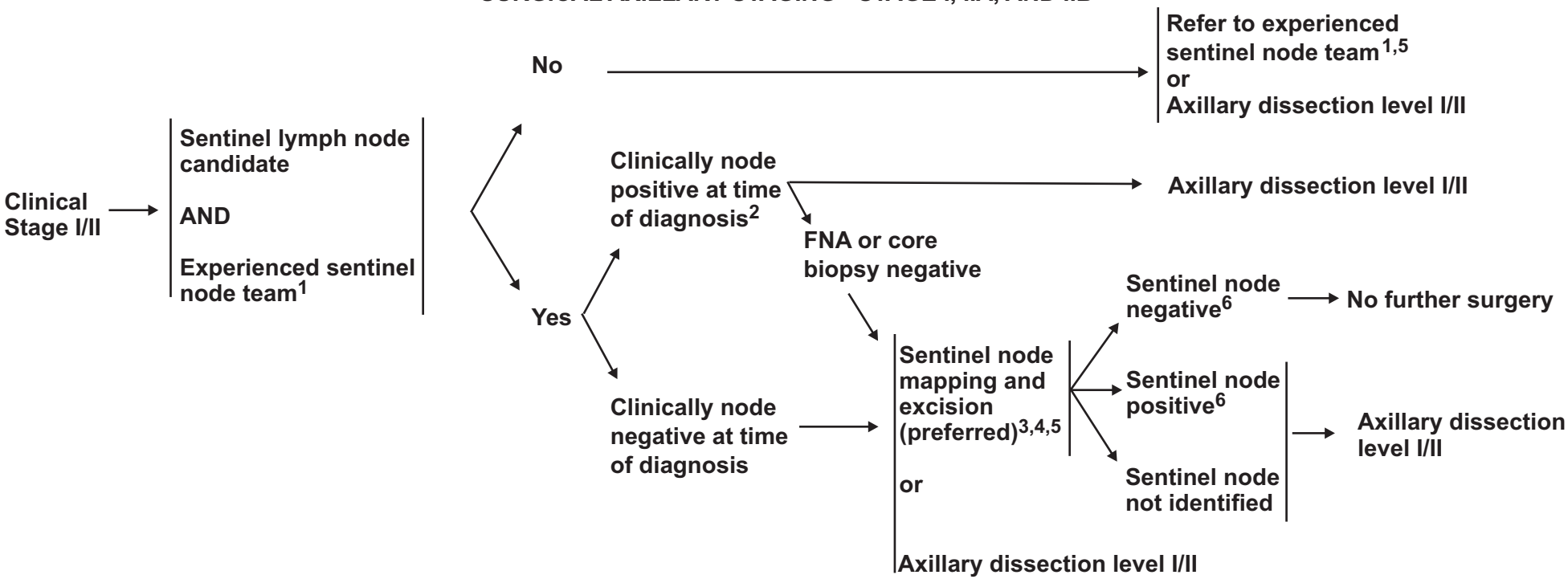
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Invasive Breast Cancer

SURGICAL AXILLARY STAGING - STAGE I, IIA, AND IIB



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

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

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

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

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

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

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Return to Locoregional Treatment (BINV-2)

AXILLARY LYMPH NODE STAGING

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

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

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MARGIN STATUS IN INFILTRATING CARCINOMA

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

It may be reasonable to treat selected cases with breast conserving therapy with a microscopically focally positive margin in the absence of an extensive intraductal component.[1] For these patients, the use of a higher radiation boost dose to the tumor bed should be considered.

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

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

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

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SPECIAL CONSIDERATIONS TO BREAST-CONSERVING THERAPY REQUIRING RADIATION THERAPY

Contraindications for breast-conserving therapy requiring radiation therapy include:

Absolute:

- **Prior radiation therapy to the breast or chest wall**
- **Radiation therapy during pregnancy**
- **Diffuse suspicious or malignant appearing microcalcifications**
- **Widespread disease that cannot be incorporated by local excision through a single incision that achieves negative margins with a satisfactory cosmetic result.**
- **Positive pathologic margin[1]**

Relative:

- **Active connective tissue disease involving the skin (especially scleroderma and lupus)**
- **Tumors > 5 cm (category 2B)**
- **Focally positive margin[1]**
- **Women ≤ 35 y or premenopausal women with a known BRCA 1/2 mutation:**
  - **May have an increased risk of ipsilateral breast recurrence or contralateral breast cancer with breast conserving therapy**
  - **Prophylactic bilateral mastectomy for risk reduction may be considered. (See NCCN Breast Cancer Risk Reduction Guidelines).**

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

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PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

- The breast can be reconstructed in conjunction with mastectomy using breast implants, autologous tissue ("flaps") or a combination of the two (e.g., latissimus / implant composite reconstructions).
- Breast reconstruction for mastectomy can be performed at the same time as mastectomy ("immediate") or at some time following the completion of cancer treatment ("delayed").
- As with any mastectomy, there is a risk of local and regional cancer recurrence, and evidence suggests skin sparing mastectomy is probably equivalent to standard mastectomy in this regard. Skin sparing mastectomy should be performed by an experienced breast surgery team that works in a coordinated, multidisciplinary fashion to guide proper patient selection for skin sparing mastectomy, determine optimal sequencing of the reconstructive procedure(s) in relation to adjuvant therapies, and to perform a resection that achieves appropriate surgical margins. Post-mastectomy radiation as outlined in these guidelines should be applied in cases treated by skin sparing mastectomy. The nipple-areolar complex is sacrificed with skin sparing mastectomy for cancer therapy.
- When post-mastectomy radiation is required, delayed reconstruction is generally preferred after completion of radiation therapy in autologous tissue reconstruction, because of reported loss in reconstruction cosmesis (category 2B). When implant reconstruction is used, immediate rather than delayed reconstruction is preferred to avoid tissue expansion of radiated skin flaps. Immediate implant reconstruction in patients requiring post-operative radiation has an increased rate of capsular contracture. Surgery to exchange the tissue expanders with permanent implants can be performed prior to radiation or after completion of radiation therapy. Some experienced breast cancer teams have employed protocols in which immediate reconstructions are followed by radiation therapy (category 2B). Tissue expansion of irradiated skin can result in a significantly increased risk of capsular contracture, malposition, poor cosmesis and implant exposure. In the previously radiated patient the use of tissue expanders/implants is relatively contra-indicated.
- Reconstruction selection is based on an assessment of cancer treatment, patient body habitus, smoking history, co-morbidities and patient concerns. Smoking increases the risk of complications for all types of breast reconstruction whether with implant or flap. Smoking is therefore considered a relative contra-indiction to breast reconstruction and patients should be made aware of increased rates of wound healing complications and partial or complete flap failure among smokers.
- An evaluation of the likely cosmetic outcome of lumpectomy should be performed prior to surgery.
- Women who are not satisfied with the cosmetic outcome following completion of breast cancer treatment should be offered a plastic surgery consultation.

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

PRINCIPLES OF RADIATION THERAPY

Whole Breast Radiation:
Target delineation includes the majority of the breast tissue, and is best done by both clinical assessment and CT-based treatment planning. A uniform dose distribution is the objective, using compensators such as wedges, forward planning using segments, or intensity modulated radiation therapy (IMRT) The breast should receive a dose of 45-50 Gy in 1.8 - 2 Gy per fraction, or 42.5 Gy at 2.66 Gy per fraction. A boost to the tumor bed is recommended in patients at higher risk for local failure, (age < 50, positive axillary nodes, lymphovascular invasion, or close margins). This can be achieved with brachytherapy or electron beam or photon fields. Typical doses are 10-16 Gy at 2 Gy/fx. All dose schedules are given 5 days per week.

Chest Wall Radiation (including breast reconstruction):
The target includes the ipsilateral chest wall, mastectomy scar, and drain sites where possible. Depending on whether the patient has been reconstructed or not, several techniques using photons and/or electrons are appropriate. CT-based treatment planning is encouraged, in order to identify lung and heart volumes, and minimize exposure of these organs. Special consideration should be given to the use of bolus material when photon fields are used, to ensure the skin dose is adequate.

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

Dose is 50 Gy, given as 1.8 - 2.0 Gy fraction size (± scar boost at 2 Gy per fraction to a total dose of approximately 60 Gy); all dose schedules given 5 days per week.
If internal mammary lymph nodes are clinically or pathologically positive, radiation therapy should be given to the internal mammary nodes, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be utilized in all cases where radiation therapy is delivered to the internal mammary lymph node field.

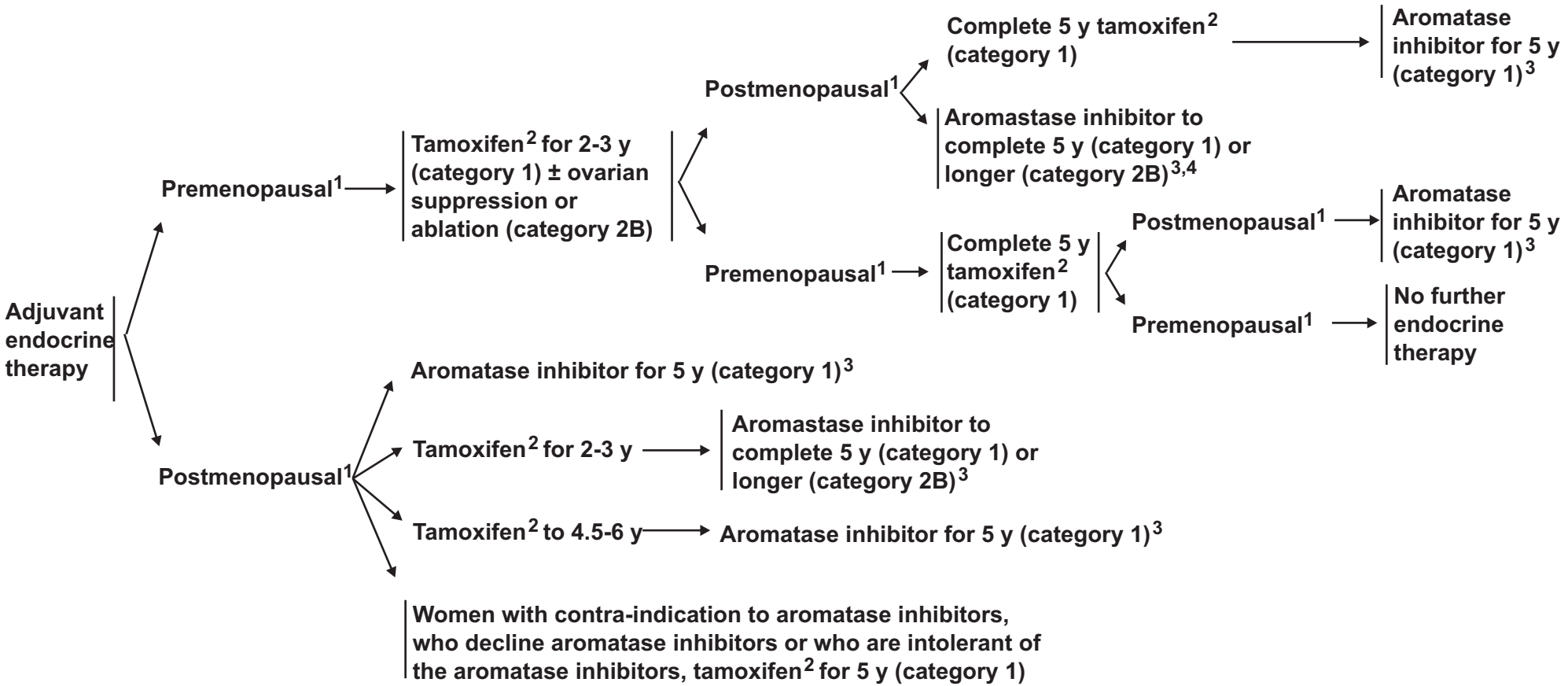
Partial breast radiation (PBI)
PBI should be performed only as part of a prospective trial. PBI can be delivered with brachytherapy or external beam radiation using 3-D conformal radiation or IMRT. If not trial eligible, PBI should be reserved for patients with a low risk of recurrence. The target includes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

Neoadjuvant chemotherapy:
Indications for radiation therapy and fields of treatment should be based upon the pretreatment tumor characteristics in patients treated with neoadjuvant 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 Cancer

ADJUVANT ENDOCRINE THERAPY



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

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

[3] The panel believes the three selective aromatase inhibitors (anastrozole, letrozole, exemestane) have similar antitumor efficacy and similar toxicity profiles. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.

[4] This specific patient subset was not included in the trials of aromatase inhibitors given sequentially with adjuvant tamoxifen. Some women who appear to become postmenopausal on tamoxifen therapy have resumption of ovarian function after discontinuation of tamoxifen and initiation of an aromatase inhibitor. Therefore, serial monitoring of plasma estradiol and FSH levels is encouraged in this clinical setting. Should ovarian function resume, the aromatase inhibitor should be discontinued and tamoxifen resumed. See Definition of Menopause (BINV-K).

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Invasive Breast Cancer

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

NON-TRASTUZUMAB CONTAINING REGIMENS (all category 1)

Preferred Adjuvant Regimens:

- **TAC (docetaxel/doxorubicin/cyclophosphamide)**
- **Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks**
- **AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel**
- **TC (docetaxel and cyclophosphamide)**
- **AC (doxorubicin/cyclophosphamide)**

Other Adjuvant Regimens:

- **FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide)**
- **FEC/CEF (cyclophosphamide/epirubicin/fluorouracil)**
- **CMF (cyclophosphamide/methotrexate/fluorouracil)**
- **AC followed by docetaxel every 3 weeks**
- **AC followed by paclitaxel every 3 weeks**
- **EC (epirubicin/cyclophosphamide)**
- **A followed by T followed by C (doxorubicin followed by paclitaxel followed by cyclophosphamide) every 2 weekly regimen with filgrastim support**
- **FEC followed by T (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel)**

TRASTUZUMAB CONTAINING REGIMENS (all category 1)

Preferred Adjuvant Regimen:

- **AC followed by T + concurrent trastuzumab (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules)**
- **TCH (docetaxel, carboplatin, trastuzumab)**

Other Adjuvant Regimens:

- **Docetaxel + trastuzumab followed by FEC (fluorouracil/epirubicin/cyclophosphamide)**
- **Chemotherapy followed by trastuzmab sequentially**
- **AC followed by docetaxel + trastuzumab**

Neoadjuvant:

- **T + trastuzumab followed by CEF + trastuzumab (paclitaxel plus trastuzumab followed by cyclophosphamide/epirubicin/fluorouracil plus trastuzumab)**

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

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

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

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

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

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

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

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.

NON-TRASTUZUMAB CONTAINING COMBINATIONS

PREFERRED ADJUVANT REGIMENS

TAC chemotherapy[1]
- Docetaxel 75 mg/m^2 IV day 1
- Doxorubicin 50 mg/m^2 IV day 1
- Cyclophosphamide 500 mg/m^2 IV day 1

Cycled every 21 days for 6 cycles.
(All cycles are with filgrastim support).

Dose-dense AC followed by paclitaxel chemotherapy[2]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 14 days for 4 cycles.
Followed by
- Paclitaxel 175 mg/m^2 by 3 h IV infusion day 1

Cycled every 14 days for 4 cycles.
(All cycles are with filgrastim support).

AC followed by paclitaxel chemotherapy[3,4,5]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 4 cycles.
- Followed by
- Paclitaxel 80 mg/m2 by 1 h IV infusion weekly for 12 wks.

TC chemotherapy[6]
- Docetaxel 75 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 4 cycles

AC chemotherapy [7]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 4 cycles.

OTHER ADJUVANT REGIMENS

FAC chemotherapy[8,9]
- 5-Fluorouracil 500 mg/m^2 IV days 1 & 8 or days 1 & 4
- Doxorubicin 50 mg/m^2 IV day 1 (or by 72 h continuous infusion)
- Cyclophosphamide 500 mg/m^2 IV day 1

Cycled every 21 days for 6 cycles.

CAF chemotherapy[10]
- Cyclophosphamide 100 mg/m^2 IV day 1
- Doxorubicin 30 mg/m^2 IV day 1 & 8
- 5-Fluorouracil 500 mg/m^2 IV days 1 & 8

Cycled every 28 days for 6 cycles.

FEC chemotherapy[11]
- Cyclophosphamide 75 mg/m^2 PO days 1-14
- Epirubicin 60 mg/m^2 IV days 1 & 8
- 5-Fluorouracil 500 mg/m^2 IV days 1 & 8

With cotrimoxazole support.
Cycled every 28 days for 6 cycles.

CMF chemotherapy [12]
- Cyclophosphamide 100 mg/m^2 PO days 1-14
- Methotrexate 40 mg/m^2 IV days 1 & 8
- 5-Fluorouracil 600 mg/m^2 IV days 1 & 8

Cycled every 28 days for 6 cycles.

AC followed by docetaxel chemotherapy[5]
- Doxorubicin 60 mg/m^2 on day 1
- Cyclophosphamide 600 mg/m2 IV day 1

Cycled every 21 days for 4 cycles.
Followed by
- Docetaxel 100 mg/m^2 IV on day 1

Cycled every 21 days for 4 cycles

AC followed by paclitaxel chemotherapy[3,4,5]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 4 cycles.
Followed by
- Paclitaxel 175-225 mg/m^2 by 3 h IV infusion day 1

Cycled every 21 days for 4 cycles.

EC chemotherapy[13]
- Epirubicin 100 mg/m^2 IV day 1
- Cyclophosphamide 830 mg/m^2 IV day 1

Cycled every 21 days for 8 cycles.

Dose-dense A-T-C chemotherapy[2]
- Doxorubicin 60 mg/m^2 IV day 1

Cycled every 14 days for 4 cycles.
Followed by
- Paclitaxel 175 mg/m^2 by 3 h IV day 1

Cycled every 14 days for 4 cycles.
Followed by
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 14 days for 4 cycles.
(All cycles are with filgrastim support).

FEC followed by docetaxel chemotherapy[14]
- 5-Fluorouracil 500 mg/m^2 IV day 1
- Epirubicin 100 mg/m^2 IV day 1
- Cyclophosphamide 500 mg/m^2 day 1

Cycled every 21 days for 3 cycles.
Followed by
- Docetaxel 100 mg/m^2 day 1

Cycled every 21 days for 3 cycles.

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TRASTUZUMAB CONTAINING COMBINATIONS

PREFERRED ADJUVANT REGIMENS

AC followed by T chemotherapy with Trastuzumab[15]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 4 cycles.
Followed by
Paclitaxel 80 mg/m2 by 1 h IV weekly for 12 wks
With
- Trastuzumab 4 mg/kg IV with first dose of paclitaxel

Followed by
- Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment. As an alternative, trastuzumab 6 mg/kg IV every 3 wk may be used following the completion of paclitaxel, and given to complete 1 y of trastuzumab treatment.

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

Dose-dense AC followed by paclitaxel chemotherapy[2]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 14 days for 4 cycles.
Followed by
- Paclitaxel 175 mg/m^2 by 3 h IV infusion day 1

Cycled every 14 days for 4 cycles.
(All cycles are with filgrastim support).
With
- Trastuzumab 4 mg/kg IV with first dose of paclitaxel

Followed by
- Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment. As an alternative, trastuzumab 6 mg/kg IV every 3 wk may be used following the completion of paclitaxel, and given to complete 1y of trastuzumab treatment.

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

AC followed by T chemotherapy with Trastuzumab[15]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 4 cycles.
Followed by
- Paclitaxel 175 mg/m^2 by 3 h IV day 1

Cycled every 21 days for 4 cycles
With
- Trastuzumab 4 mg/kg IV with first dose of paclitaxel

Followed by
- Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment. As an alternative, trastuzumab 6 mg/kg IV every 3 wk may be used following the completion of paclitaxel, and given to complete 1y of trastuzumab treatment.

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

TCH chemotherapy[16]
- Docetaxel 75 mg/m^2 IV day 1

Followed by
- Carboplatin AUC 6 IV day 1

Cycled every 21 days for 6 cycles
With
- Trastuzumab 4 mg/kg wk 1

Followed by
- Trastuzumab 2 mg/kg for 17 wks

Followed by
- Trastuzumab 6 mg/kg IV every 3 wks to complete 1 year of trastuzumab therapy

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

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

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OTHER ADJUVANT REGIMENS

Docetaxel + trastuzumab followed by FEC chemotherapy[17]
- Docetaxel 100 mg/m^2 by 1 h IV day 1

Cycled every 21 days for 3 cycles
With
- Trastuzumab 4 mg/kg IV with first dose of docetaxel day 1

Followed by
- Trastuzumab 2 mg/kg IV weekly to complete 9 wks of trastuzumab.

Followed by
- 5-Fluorouracil 600 mg/m^2 IV day 1
- Epirubicin 60 mg/m^2 day 1
- Cyclophosphamide 600 mg/m^2 day 1

Cycled every 21 days for 3 cycles
Cardiac monitoring at baseline, after last FEC cycle, at 12 and 36 mo after chemotherapy.

Chemotherapy followed by trastuzumab[18]
- Approved adjuvant chemotherapy regimen for at least 4 cycles

Followed by
- Trastuzumab 8 mg/kg IV times 1 dose

Followed by
- Trastuzumab 6 mg/kg IV every 21 days for 1 y

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

AC followed by docetaxel chemotherapy with trastuzumab[17]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 day 1

Cycled every 21 days for 4 cycles
Followed by
- Docetaxel 100 mg/m^2

Cycled every 21 days for 4 cycles
With
- Trastuzumab 4 mg/kg IV wk one

Followed by
- Trastuzumab 2 mg/kg IV weekly for 11 wks

Followed by
- Trastuzumab 6 mg/kg every 21 days to complete 1 y of trastuzumab therapy

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

TRASTUZUMAB CONTAINING COMBINATIONS

NEOADJUVANT REGIMENS

Neoadjuvant T followed by FEC chemotherapy with trastuzumab[19]
- Trastuzumab 4 mg/kg IV for one dose beginning just prior to first dose of paclitaxel

Followed by
- Trastuzumab 2 mg/kg IV weekly for 23 wks
- Paclitaxel 225 mg/m^2 by 24 h IV infusion every 21 days for 4 cycles (alternatively paclitaxel may be administered as paclitaxel 80 mg/m^2 by 1 h IV infusion weekly for 12 wks)

Followed by
- 5-Fluorouracil 500 mg/m^2 on days 1 and 4
- Epirubicin 75 mg/m^2 IV on day 1
- Cyclophosphamide 500 mg/m^2 on day 1

Cycled every 21 days for 4 cycles.

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

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

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DEFINITION OF MENOPAUSE

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

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

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

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SUBSEQUENT ENDOCRINE THERAPY FOR SYSTEMIC DISEASE

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

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

POSTMENOPAUSAL PATIENTS

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

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

REGIMENS FOR METASTATIC DISEASE[1]

PREFERRED SINGLE AGENTS

Anthracyclines
- Doxorubicin
- Epirubicin
- Pegylated liposomal doxorubicin

Taxanes
- Paclitaxel
- Docetaxel
- Albumin-bound paclitaxel

Anti-metabolites
- Capecitabine
- Gemcitabine

Other microtubule inhibitors
- Vinorelbine

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

PREFERRED AGENTS WITH BEVACIZUMAB
- Paclitaxel[2]

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

OTHER COMBINATIONS
- Ixabepilone + capecitabine (category 2B)

PREFERRED FIRST-LINE AGENTS FOR HER2-POSITIVE DISEASE

Trastuzumab with:
- Paclitaxel ± carboplatin
- Docetaxel
- Vinorelbine
- Capecitabine

PREFERRED AGENTS FOR TRASTUZUMAB-EXPOSED HER2-POSITIVE DISEASE
- Lapatinib + capecitabine
- Trastuzumab + other first-line agents
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)

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

[2]A single randomized clinical trial documents superior time to progression with the combination of bevacizumab plus paclitaxel compared with paclitaxel alone for first line chemotherapy of metastatic disease.

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 COMBINATIONS

CAF chemotherapy[1]
- Cyclophosphamide 100 mg/m^2 PO days 1-14
- Doxorubicin 30 mg/m^2 IV days 1 & 8
- 5-Fluorouracil 500 mg/m^2 IV days 1 & 8

Cycled every 28 days.

FAC chemotherapy[2]
- 5-Fluorouracil 500 mg/m^2 IV days 1 & 8 or days 1 & 4
- Doxorubicin 50 mg/m^2 IV day 1
- Cyclophosphamide 500 mg/m^2 IV day 1

Cycled every 21 days.

FEC chemotherapy[3]
- Cyclophosphamide 400 mg/m^2 IV days 1 & 8
- Epirubicin 50 mg/m^2 IV days 1 & 8
- 5-Fluorouracil 500 mg/m^2 IV days 1 & 8

Cycled every 28 days.

AC chemotherapy[4]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days.

EC chemotherapy[5]
- Epirubicin 75 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m2 IV day 1

Cycled every 21 days

AT chemotherapy[6]
- Doxorubicin 60 mg/m^2 IV day 1
- Paclitaxel 125-200 mg/m^2 IV day 1

Cycled every 21 days

AT chemotherapy[7]
- Doxorubicin 50 mg/m^2 IV day 1
- Docetaxel 75 mg/m2 IV day 1

Cycled every 21 days

CMF chemotherapy[8]
- Cyclophosphamide 100 mg/m^2 PO days 1-14
- Methotrexate 40 mg/m^2 IV days 1 & 8
- 5-Fluorouracil 600 mg/m^2 IV days 1 & 8

Cycled every 28 days.

Docetaxel/capecitabine chemotherapy[9]
- Docetaxel 75 mg/m^2 IV day 1
- Capecitabine 950 mg/m^2 PO twice daily days 1-14

Cycled every 21 days.

GT chemotherapy[10]
- Paclitaxel 175 mg/m^2 IV day 1
- Gemcitabine 1250 mg/m^2 IV days 1 & 8 (following paclitaxel on day 1)

Cycled every 21 days.

OTHER COMBINATIONS

Ixabepilone/capecitabine (category 2B)
- Ixabepilone 40 mg/m^2 IV day 1
- Capecitabine 2000 mg/m^2 PO days 1-14

Cycled every 21 days.

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PREFERRED SINGLE AGENTS

Anthracyclines:

Doxorubicin 60-75 mg/m^2 IV day 1[11]
Cycled every 21 days
OR
- **Doxorubicin 20 mg/m^2 IV weekly[12]**

- **Epirubicin 60-90 mg/m^2 IV day 1[13]**
Cycled every 21 days.

- **Pegylated liposomal encapsulated doxorubicin 50 mg/m^2 IV day 1[14]**
Cycled every 28 days.

Taxanes:

- **Paclitaxel 175 mg/m^2 IV day 1[15]**
Cycled every 21 days.
OR
- **Paclitaxel 80 mg/m^2 IV weekly[16]**

- **Docetaxel 60-100 mg/m^2 IV day 1[17,18]**
Cycled every 21 days.
OR
- **Docetaxel 40 mg/m^2 IV weekly for 6 wks followed by a 2 week rest, then repeat[19]**

- **Albumin-bound paclitaxel 100 mg/m^2 or 150 mg/m^2 days 1, 8, and 15 IV [20,21]**
Cycled every 28 days.

Albumin-bound paclitaxel 260 mg/m^2 IV[20]
Cycled every 21 days.

Anti-metabolites:

- **Capecitabine 1000-1250 mg/m^2 PO twice daily days 1-14 [22]**
Cycled every 21 days.

- **Gemcitabine 800-1200 mg/m^2 IV days 1, 8 & 15 [23]**
Cycled every 28 days.

Other microtubule inhibitors:

- **Vinorelbine 25 mg/m2 IV weekly[24]**

OTHER SINGLE AGENTS

- **Cyclophosphamide**
- **Mitoxantrone**
- **Cisplatin**
- **Etoposide (PO) (category 2B)**
- **Vinblastine**
- **Fluorouracil CI**
- **Ixabepilone**

PREFERRED AGENTS WITH BEVACIZUMAB

Paclitaxel plus bevacizumab[25]
- **Paclitaxel 90 mg/m^2 by 1 h IV days 1, 8 & 15**
- **Bevacizumab 10 mg/kg IV days 1 & 15**

Cycled every 28 days.

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PREFERRED FIRST-LINE AGENTS WITH TRASTUZUMAB FOR HER2-POSITIVE DISEASE

COMBINATIONS

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

Cycled every 21 days.

Weekly TCH chemotherapy[27]
- Paclitaxel 80 mg/m^2 IV days 1, 8 & 15
- Carboplatin AUC of 2 IV days 1, 8 & 15

Cycled every 28 days.

SINGLE AGENTS

- Paclitaxel 175 mg/m^2 IV day 1[28]

Cycled every 21 days.
OR
- Paclitaxel 80-90 mg/m^2 IV weekly[29]

- Docetaxel 80 to 100 mg/m^2 IV day 1[30]

Cycled every 21 days
OR
- Docetaxel 35 mg/m^2 IV infusion weekly[31]

- Vinorelbine 25 mg/m^2 IV weekly[32]

- Capecitabine 1000-1250 mg/m^2 PO twice daily days 1-14 [33]

Cycled every 21 days

TRASTUZUMAB COMPONENT

Trastuzumab 4 mg/kg IV day 1
Followed by
2 mg/kg IV weekly[28,37]
OR
Trastuzumab 8 mg/kg IV day 1
Followed by
6 mg/kg IV every 3 wks[38]

PREFERRED AGENTS FOR TRASTUZUMAB-EXPOSED HER2-POSITIVE DISEASE

Capecitabine plus lapatinib[34]
- Capecitabine 1000 mg/m^2 PO twice daily Days 1 - 14
- Lapatinib 1250 mg PO daily Days 1-21

Cycled every 21 days

Trastuzumab + other first-line agents

Trastuzumab + capecitabine[35]

Trastuzumab + lapatinib[36]
- Lapatinib 1000 mg PO daily

TRASTUZUMAB COMPONENT

Trastuzumab 4 mg/kg IV day 1
Followed by
2 mg/kg IV weekly[28,37]
OR
Trastuzumab 8 mg/kg IV day 1
Followed by
6 mg/kg IV every 3 wks[38]

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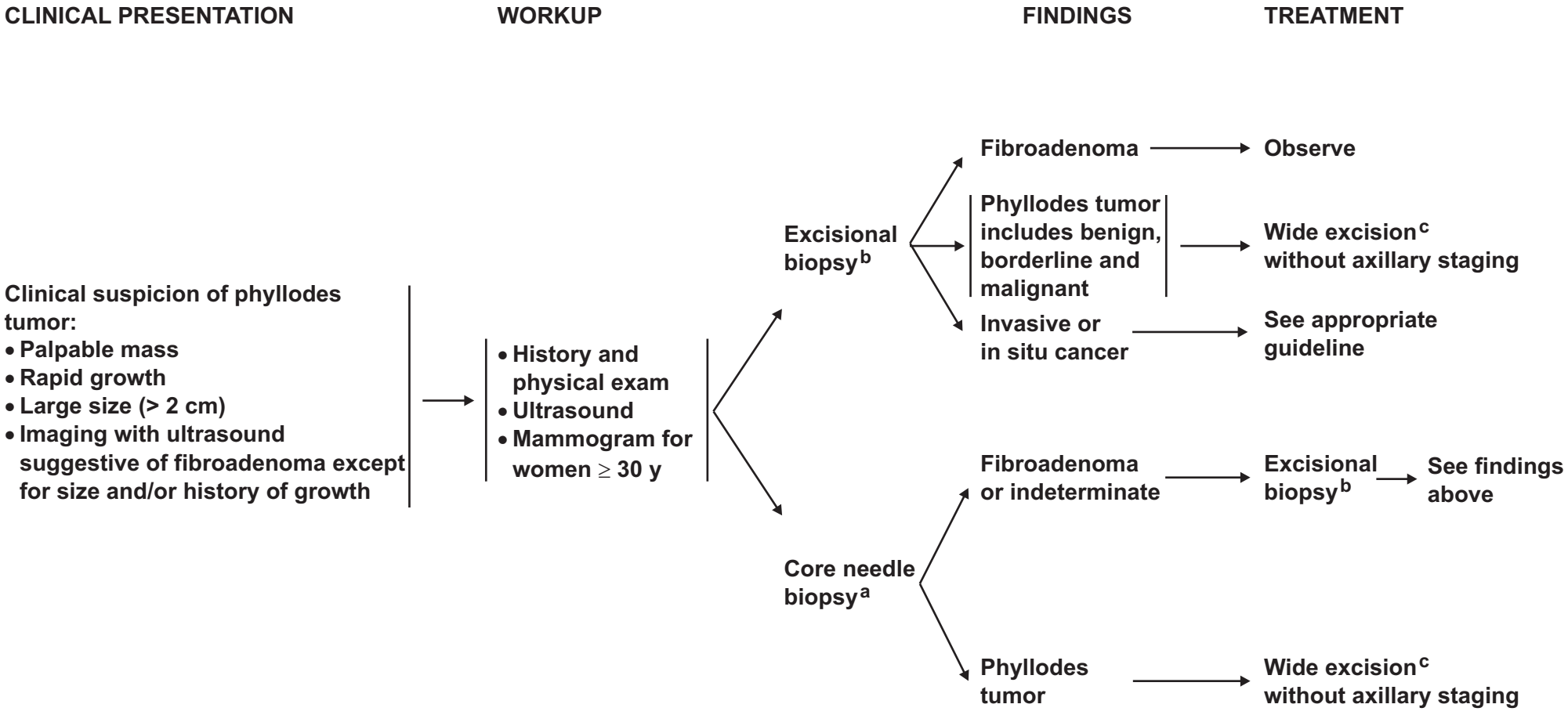
Phyllodes Tumor



[a]FNA will not, and core biopsy may not distinguish fibroadenoma from phyllodes tumor in most cases.
[b]Excisional biopsy includes complete mass removal, but without the intent of obtaining surgical margins.
[c]Wide excision means exision with the intention of obtaining surgical margins ≥ 1 cm. Narrow surgical margins are associated with heightened local recurrence risk, but are not an absolute indication for mastectomy when partial mastectomy fails to achieve margin width ≥ 1 cm.

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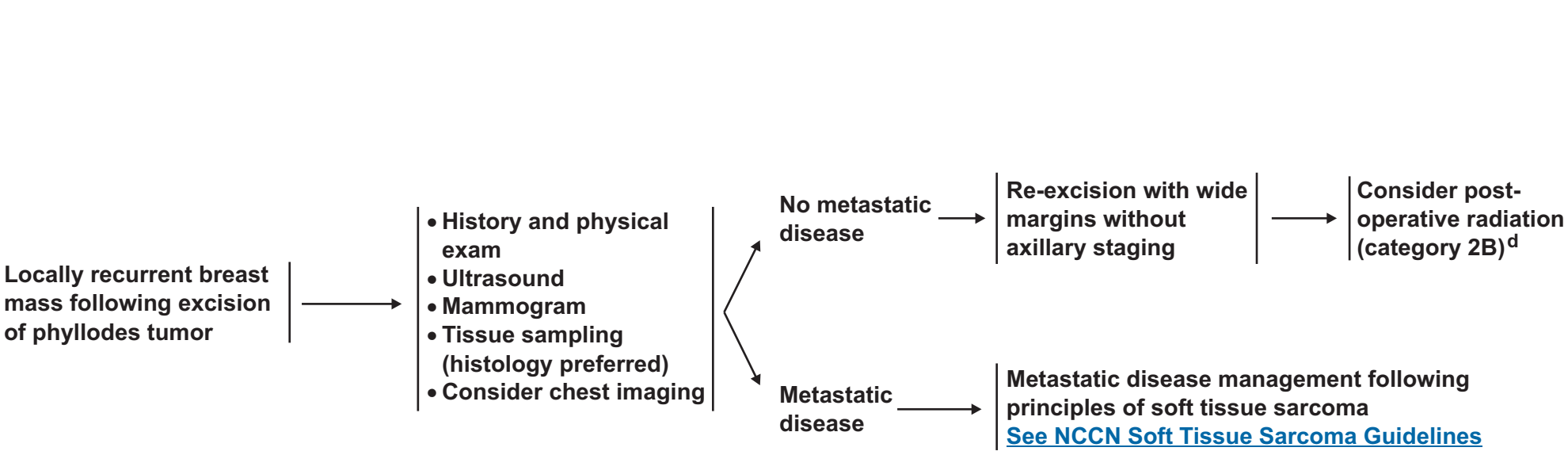
Phyllodes Tumor

PHYLLODES TUMOR RECURRENCE



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

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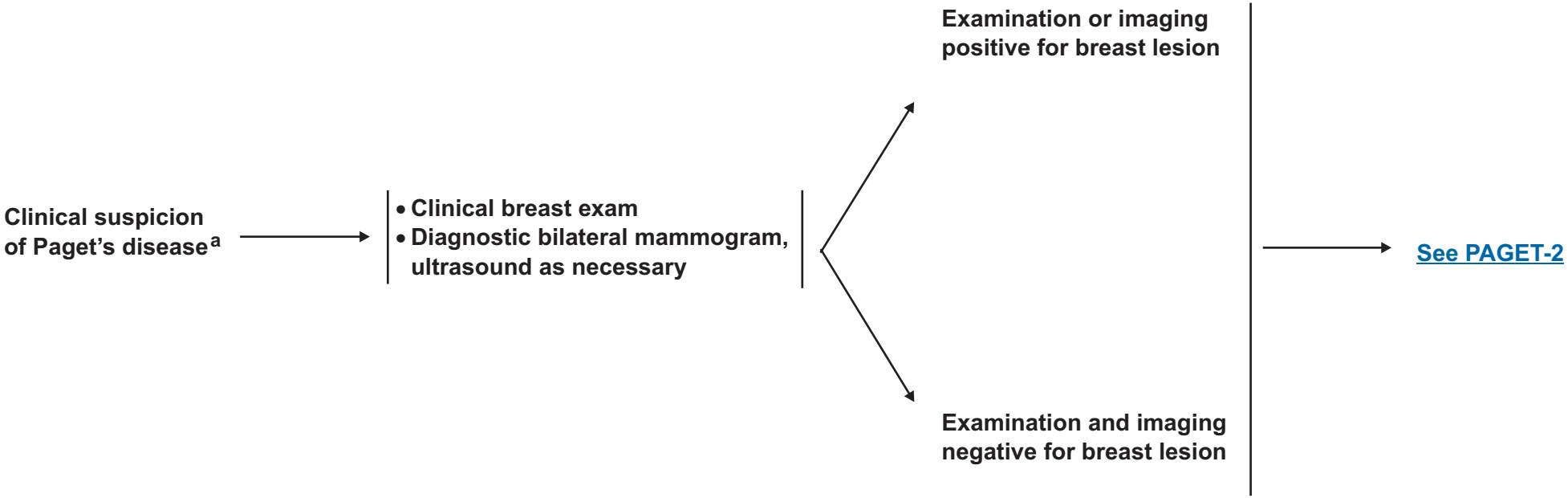
Paget's Disease

CLINICAL PRESENTATION

WORKUP



[a]Nipple or areolar eczema, ulceration, bleeding, itching.

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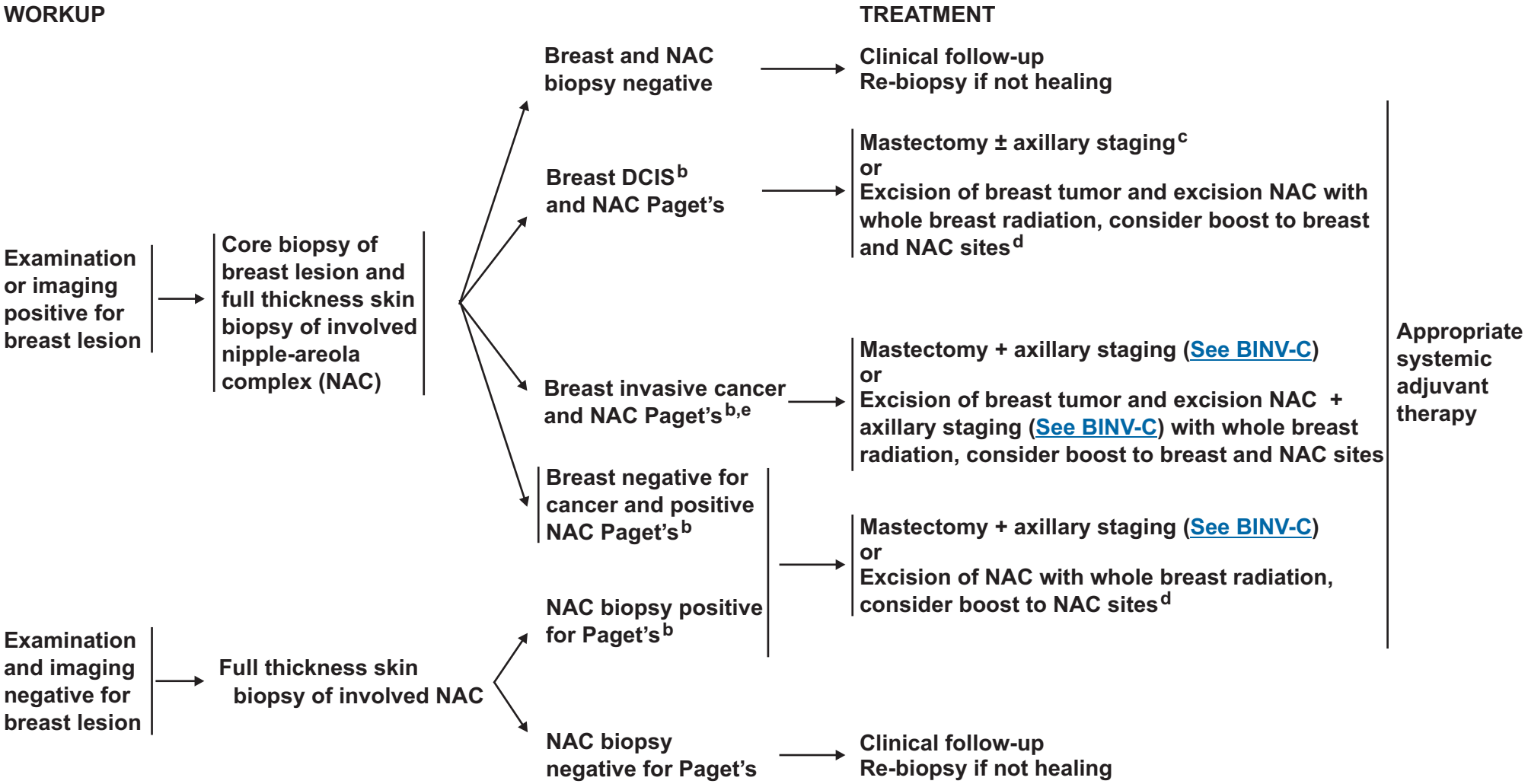
Paget's Disease



[b] To assess extent of disease or confirm additional disease consider MRI (See BINV-B).
[c] Mastectomy is always an option with any manifestation of Paget's disease (see manuscript text).
[d] With Paget's disease and no associated peripheral cancer, or with associated DCIS, consider tamoxifen 20 mg per day for 5 years.
[e] With associated invasive breast cancer, treat with appropriate systemic adjuvant therapy (See BINV-4)

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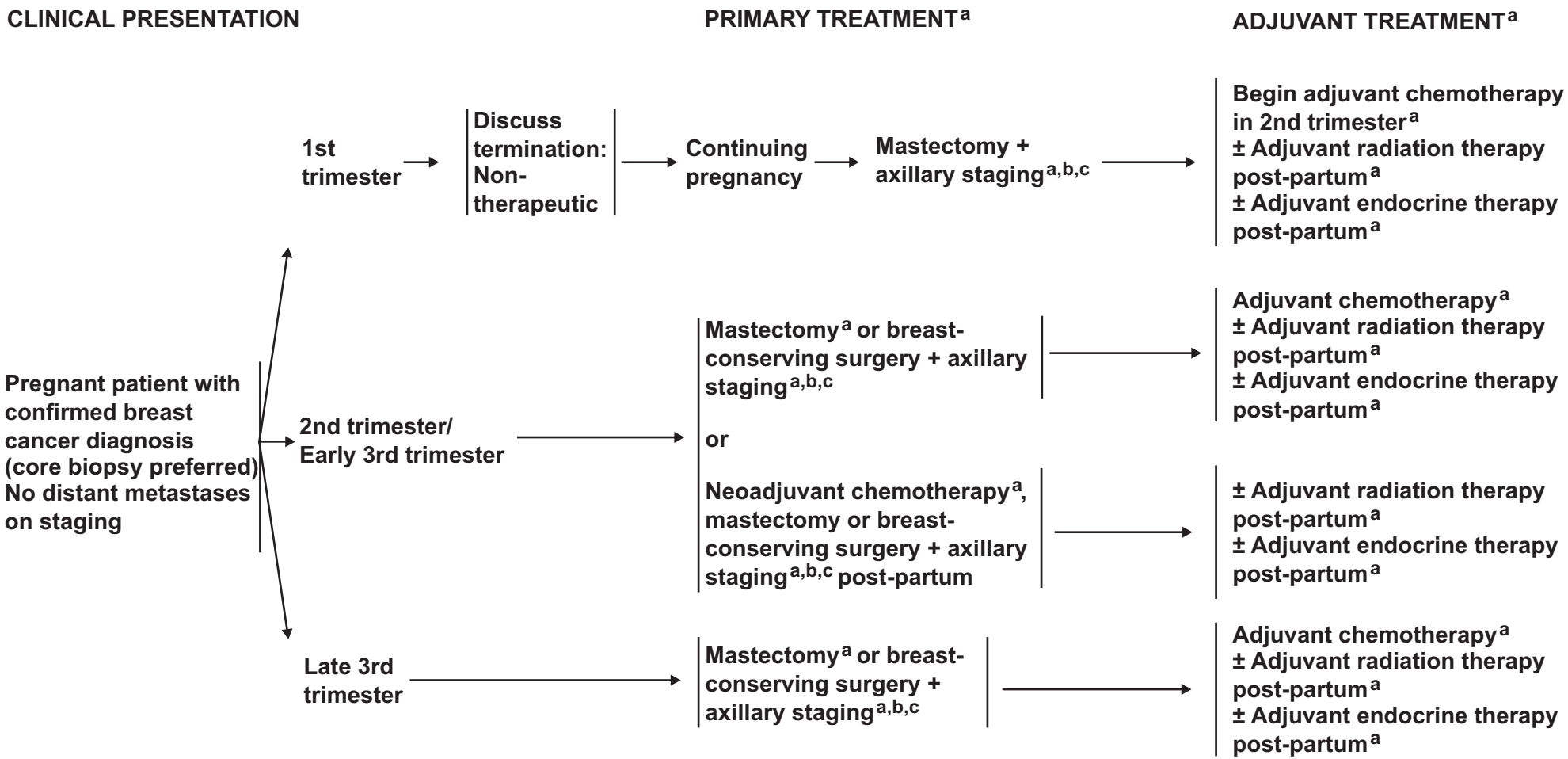
Breast Cancer During Pregnancy



[a] Considerations and selection of optimal local therapy and systemic therapy are similar to that recommended in non-pregnancy associated breast cancer, see other sections of this guideline. However, the selection and timing of chemotherapy, endocrine therapy, and radiation therapy is different in the pregnant versus non-pregnant patient. Please see discussion section. Chemotherapy should not be administered during the first trimester of pregnancy and radiation therapy should not be administered during any trimester of pregnancy. Most experience with chemotherapy during pregnancy for breast cancer is from regimens that utilize various combinations of doxorubicin, cyclophosphamide and fluorouracil. Consideration for post-partum chemotherapy are the same as for non-pregnancy associated breast cancer.

[b] See Surgical Axillary Lymph Node Staging (BINV-C).

[c] There are insufficient safety data to recommend general use of sentinel node procedures, a taxane or trastuzumab during pregnancy.

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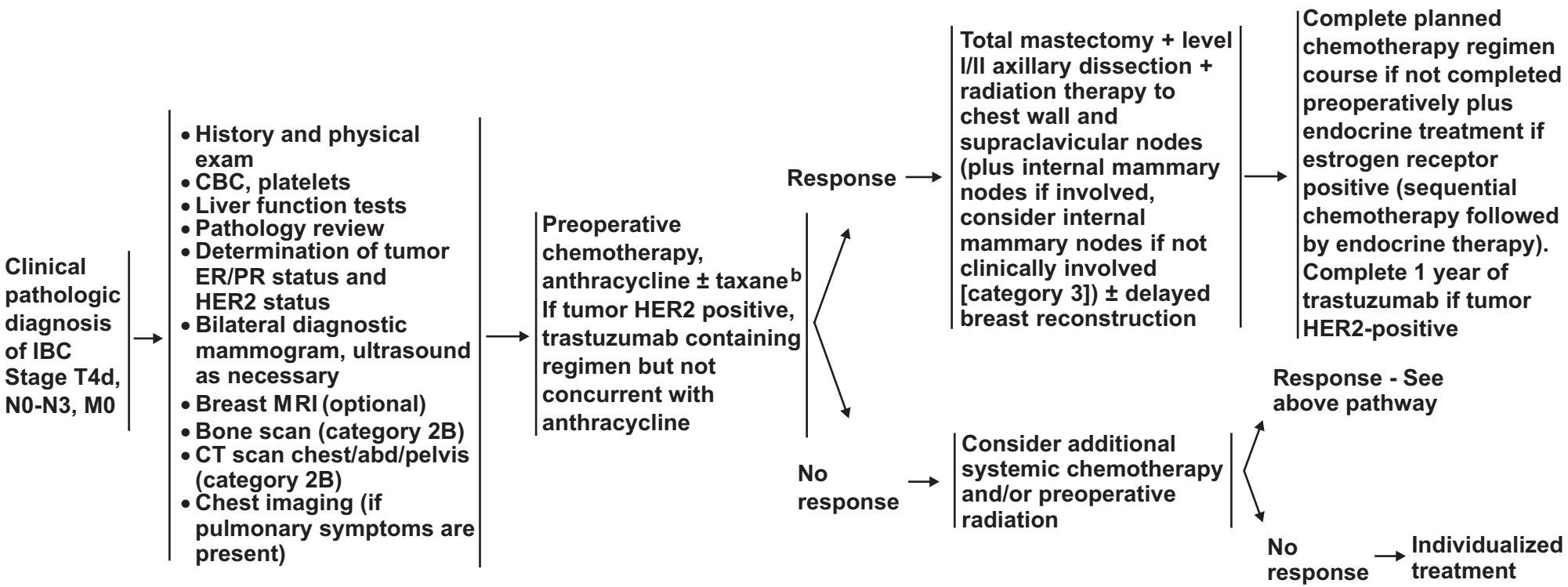
Inflammatory Breast Cancer



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

[b] Patients with HER2-positive tumors should be considered for chemotherapy incorporating trastuzumab (See BINV-J).

[c] See Principles of Reconstruction Following Surgery (BINV-G).

[d] Patients with stage IV or recurrent IBC should be treated according to the guideline for recurrence/stage IV disease (BINV-15 to BINV-20).

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Staging

Table 1

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

Primary Tumor (T)

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

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

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

T1		Tumor 2 cm or less in greatest dimension
	T1mic	Microinvasion 0.1 cm or less in greatest dimension
	T1a	Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
	T1b	Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
	T1c	Tumor more than 1 cm but not more than 2 cm in greatest dimension
T2		Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3		Tumor more than 5 cm in greatest dimension
T4		Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below
	T4a	Extension to chest wall, not including pectoralis muscle
	T4b	Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
	T4c	Both T4a and T4b
	T4d	Inflammatory carcinoma

Regional Lymph Nodes (N)

Clinical

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

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

Staging continued on next page (ST-2)

Table 1 (continued)

Pathologic (pN)[a]

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

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

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

- pN0(i-) No regional lymph node metastasis histologically, negative IHC
- pN0(i+) No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm
- pN0(mol-) No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)[b]
- pN0(mol+) No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)[b]

[a]Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary node dissection is designated (sn) for "sentinel node," e.g., pN0(i+) (sn).

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

pN1 Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not *clinically apparent***

- pN1mi Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
- pN1a Metastasis in 1 to 3 axillary lymph nodes
- pN1b Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not *clinically apparent***
- pN1c Metastasis in 1 to 3 axillary lymph nodes and in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not *clinically apparent*.** (If associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden)

pN2 Metastasis in 4 to 9 axillary lymph nodes, or in *clinically apparent** internal mammary lymph nodes in the *absence* of axillary lymph node metastasis

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

pN3 Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in *clinically apparent** ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes

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

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

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

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

* T1 includes T1mic

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

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

HISTOPATHOLOGIC TYPE

The histopathologic types are the following:

In situ Carcinomas

NOS (not otherwise specified)
Intraductal
Paget's disease and intraductal

Invasive Carcinomas

NOS
Ductal
Inflammatory
Medullary, NOS
Medullary with lymphoid stroma
Mucinous
Papillary (predominantly micropapillary pattern)
Tubular
Lobular
Paget's disease and infiltrating
Undifferentiated
Squamous cell
Adenoid cystic
Secretory
Cribriform

HISTOPATHOLOGIC GRADE (G)

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

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

Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

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

The American Cancer Society estimates that 184,450 new cases of invasive breast cancer will be diagnosed and 40,930 will die of breast cancer in the United States in 2008.[1] In addition, about 67,770 women with be diagnosed with carcinoma in situ of the breast during the same year. 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,[1,2] suggesting a benefit from early detection and more effective treatment.

The etiology of the vast majority of breast cancer cases is unknown. However, numerous risk factors for the disease have been established. These risk factors include: female gender; increasing patient age; family history of breast cancer at a young age; early menarche; late menopause; older age at first live childbirth; prolonged hormone replacement therapy; previous exposure to therapeutic chest wall irradiation; benign proliferative breast disease; and genetic mutations such as of the *BRCA1/2* genes. However, except for female gender and increasing patient age, these risk factors are associated with only a minority of breast cancers. Women with a strong family history of breast cancer should be evaluated according to the NCCN Genetic/Familial High-Risk Assessment Guidelines. Women at increased risk for breast cancer (generally those with ≥1.67% 5-year risk of breast cancer using the Gail model of risk assessment [3]) may consider risk reduction strategies (see NCCN Breast Cancer Risk Reduction Guidelines).

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.[4] Approximately 85% to 90% of invasive carcinomas are ductal in origin. The invasive ductal carcinomas include unusual variants of breast cancer, such as colloid or mucinous, adenoid cystic, and tubular carcinomas, which have especially favorable natural histories.

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).[5, 6] This revision differs from the 1997 edition of the AJCC staging by incorporating the increasing use of novel imaging and pathology techniques employed at diagnosis (eg, sentinel node biopsy and immunohistochemistry [IHC] evaluation of nodes) and the number of lymph nodes involved as a factor in staging allocation. The most substantial changes are:

1. Micrometastases to ipsilateral axillary lymph nodes are distinguished from isolated tumor cells on the basis of size and histological evidence of malignant activity. All metastatic lesions to ipsilateral axillary lymph nodes no larger than 0.2 mm, whether detected by hematoxylin and eosin (H&E) staining or IHC, will be described as pN0(i+). pN0(i-) is used to indicate no detectable tumor cells by either H&E or IHC. The designation pN1mi with no additional identifiers will be used for micrometastases greater than 0.2 mm but no greater than 2.0 mm in greatest dimension.[7]
2. Identifiers are added to indicate the use of sentinel lymph node resection and IHC or molecular pathology techniques.
3. The number of involved nodes as determined by routine H&E staining (preferred method) or by IHC staining impacts pathologic N staging (pN1 if 1 to 3 lymph nodes, pN2 if 4 to 9 lymph nodes, and pN3 if 10 or more lymph nodes are involved).
4. Metastases to infraclavicular nodes are categorized as N3 disease.
5. Metastases to internal mammary (IM) nodes impact staging according to the method of detection and presence or absence of concomitant axillary lymph node involvement (N1 disease if involved IM lymph nodes are detected exclusively using sentinel lymph node detection procedure; N2 disease if detected using any other imaging study or clinical examination; or N3 disease if concomitant axillary lymph node involvement is present).
6. Metastasis to ipsilateral supraclavicular lymph nodes is no longer considered M1 disease and is classified as N3 disease.

Although determination of the specific TNM status has become more complex (especially with regard to lymph node staging), the allocation of specific TNM combinations to different stage groupings remains the same, with the exception of the creation of stage IIIC to specifically identify patients with TanyN3M0 disease. This revised staging system recognizes the heterogeneity of breast cancer and the need to create uniform data collection standards to better assess both the long-term outcome of specific patient subgroups and the impact of novel imaging or pathology techniques.[6]

Pathology Assessment

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

include failure to orient and report surgical margins, and failure to report tumor grade consistently.

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

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

Treatment Approach

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

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

Pure Noninvasive Carcinomas (Stage 0)

Both LCIS and DCIS may be difficult to distinguish from atypical hyperplasia or from carcinomas with early invasion.[12,13] Therefore, pathology review of all cases is recommended. Bilateral diagnostic mammography should be performed to identify the presence of multiple primary tumors and to estimate the extent of the noninvasive lesion. Diagnostic evaluation of LCIS is described in the NCCN Breast Screening and Diagnosis Guidelines. Genetic counseling is recommended if the patient is considered to be at high risk of hereditary breast cancer as defined by the NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Guidelines. Testing for genetic mutations without formal genetic counseling is discouraged.

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

Lobular carcinoma in situ

Observation alone is the preferred option for women diagnosed with LCIS because their risk of developing invasive carcinoma is low

(approximately 21% over 15 years).[14] The histologies of the invasive carcinomas tend to be favorable, and deaths from second invasive cancers are unusual in appropriately monitored women.[15] Bilateral mastectomy, with or without reconstruction, should be considered in special circumstances such as in women with a *BRCA*1/2 mutation or a strong family history of breast cancer. The consensus of the Panel is that consideration of a risk-reduction mastectomy is an option for a woman with LCIS without additional risk factors; however, it is not a recommended approach for most of these women. Individualized decision-making relating to the choice of a risk-reduction mastectomy for a woman with LCIS should be made only following careful evaluation and multidisciplinary counseling (see NCCN Breast Cancer Risk Reduction Guidelines).

The risk of an invasive breast cancer after a diagnosis of LCIS is equal in both breasts.[16] If mastectomy is considered as a risk reduction strategy, then a bilateral procedure is required to optimally minimize risk. Women treated with bilateral mastectomy are appropriate candidates for breast reconstruction (see BINV-G).

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

Women with LCIS, whether they undergo observation only or are treated with bilateral mastectomy, have an excellent prognosis. Recent data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial show that tamoxifen given for 5 years is associated with an approximately 46% reduction (hazard ratio 0.54; 95% CI 0.27-1.02) in the risk of developing invasive breast cancer among women with LCIS.[18,19] Results from the NSABP Study of Tamoxifen and Raloxifene (STAR) trial have shown raloxifene to be as effective as tamoxifen in reducing the risk of invasive cancer in postmenopausal patients with LCIS.[20] Therefore, the use of tamoxifen in premenopausal women or tamoxifen or raloxifene in postmenopausal women should be considered as a risk reduction strategy in women with LCIS who are followed with observation (category 1). (For recommendations on risk reduction, see also the NCCN Breast Cancer Risk Reduction Guidelines.)

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

Ductal carcinoma in situ

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

Prospective randomized trials have shown that the addition of whole breast irradiation to a margin-free excision of pure DCIS decreases the rate of in-breast disease recurrence, but does not affect overall

survival[22-24] or distant metastasis-free survival.[25] The use of whole breast radiation after breast-conserving surgery reduces the relative risk of a local failure by approximately one 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.

There is retrospective evidence suggesting that selected patients have a low risk of in-breast recurrence with excision alone without breast irradiation.[26-29] For example, in a retrospective review, 10-year disease-free survival rates of 186 patients with DCIS treated with breast-conserving surgery alone were 94% for patients with low risk DCIS and 83% for patients with both intermediate and high-risk DCIS.[28] In another retrospective study of 215 patients with DCIS treated with breast-conserving therapy without radiation therapy, endocrine therapy or chemotherapy, the recurrence rate over 8 years was 0%, 21.5%, and 32.1% in patients with low, intermediate or high risk DCIS, respectively.[29] A multi-institutional prospective study of patients with low-risk DCIS treated without radiation has also provided some support for the use of excision without radiation for DCIS.[30] In the latter study, the risk of ipsilateral breast recurrence at 5 years was 6.8% in the subset of patients with low/intermediate grade DCIS with a median tumor size of 6mm, and a median surgical margin of 5-10 mm. A higher rate of local ipsilateral recurrence (13.7%) was observed in the group of patients with small, high-grade DCIS. In both groups, the ipsilateral recurrences were approximately equally divided between DCIS and invasive cancer.

Many factors, including patient age, tumor size, tumor grade, and margin width, impact recurrence risk. The definition of a negative margin has not been firmly established in DCIS. There appears to be a consensus that margins greater than 10 mm are adequate and margins less than 1 mm are inadequate, but no uniform consensus exists for margin status between these values. Results from a retrospective study of 445 patients with pure DCIS treated by excision alone indicated that margin width was the most important independent predictor of local recurrence, although the trend for decreasing local recurrence risk with increasing margin width was most apparent with margins less than 1mm and greater than or equal to 6 mm.[31] Further complicating the issue of margin width is the impact of the fibroglandular boundary – the pectoral fascia and the superficial skin where narrower tumor free margins may provide adequate local control. Finally, because the choice of local treatment does not impact disease-related survival, the individual patient's acceptance of the potential for an increased risk of local recurrence must be considered.

Axillary dissection is not recommended for patients with pure DCIS, and axillary nodal involvement in DCIS is rare.[32] However, a small proportion of women with apparent pure DCIS on initial biopsy will be found to have invasive breast cancer at the time of the definitive surgical procedure and thus ultimately require axillary lymph node staging. In patients with apparent pure DCIS to be treated with mastectomy or with excision in an anatomic location (eg, tail of the breast), which could compromise the performance of a future sentinel lymph node procedure, a sentinel lymph node procedure may be considered.[33-35]

The primary treatment options for women with DCIS along with their respective categories of consensus are:

1) Lumpectomy plus radiation (category 1);
2) Total mastectomy, with or without reconstruction (category 2A);
3) Lumpectomy alone followed by clinical observation (category 2B).

There is no evidence that survival differs between the three treatment options. Decreased rates of local recurrence following lumpectomy have been observed in randomized trials with the addition of whole

breast radiation (category 1). Although randomized trials evaluating the effectiveness of total mastectomy in DCIS have not been performed, mastectomy is a highly effective strategy to decrease risk of local recurrence (category 2A). The option of lumpectomy alone should be considered only in cases where the patient and the physician view the individual risks as "low" (category 2B).

An analysis of specimen margins and specimen radiographs should be performed to ensure that all mammographically detectable DCIS has been excised. In addition, a post-excision mammogram should be considered where appropriate (eg, the mass and/or microcalcifications are not clearly within the specimen). Clips are used by some NCCN institutions to demarcate the biopsy area because DCIS may be clinically occult and further surgery may be required, pending the margin status review by pathology.

DCIS falls between atypical ductal hyperplasia and invasive ductal carcinoma within the spectrum of breast proliferative abnormalities. The NSABP Breast Cancer Prevention Trial showed a 75% reduction in the occurrence of invasive breast cancer in patients with atypical ductal hyperplasia treated with tamoxifen.[18,19] These data also showed that tamoxifen led to a substantial reduction in the risk of developing benign breast disease.[36] The Early Breast Cancer Trialists' overview analysis showed that, with 5 years of tamoxifen therapy, women with ER-positive or receptor-unknown invasive tumors had a 39% reduction in the annual odds of recurrence of invasive breast cancer.[2]

Similarly, the NSABP B-24 trial found a benefit from tamoxifen for women with DCIS after treatment with breast conservation surgery and radiation therapy. In that study, women with DCIS who were treated with breast-conserving therapy were randomized to receive placebo or tamoxifen. The women treated with tamoxifen had a 5% absolute reduction in recurrence risk and a 37% reduction in relative risk. The women receiving tamoxifen had an 8.2% total incidence of breast cancer (4.1% invasive and 4.2% noninvasive) compared with a 13.4% incidence of breast cancer (7.2% invasive and 6.2% noninvasive) in the placebo-treated women at a median follow-up of 74 months.[37] The cumulative incidence of invasive breast cancer at 5 years in the ipsilateral breast was 4.2% and 2.1% in women receiving placebo and tamoxifen, respectively, and in the contralateral breast, 2.3% and 1.8% in the placebo and tamoxifen groups, respectively). A retrospective analysis of ER expression in NSABP B-24 suggests that increased levels of ER expression predict for tamoxifen benefit in terms of reduction of risk for the development of both ipsilateral and contralateral breast cancer following breast-conserving therapy.[38]

Tamoxifen treatment, therefore, may be considered as a strategy to reduce the risk of ipsilateral breast cancer recurrence in women with DCIS treated with breast-conserving therapy, especially in those with ER-positive DCIS (category 1 for those undergoing breast-conserving surgery plus radiation therapy; category 2A for those undergoing excision alone). Tamoxifen may also be considered as a risk reduction therapy to decrease risk of contralateral breast cancer in women with DCIS who have undergone a lumpectomy (with or without radiation) and in women with DCIS treated with mastectomy (category 2B).

Follow-up of women with DCIS includes a physical examination every 6 to 12 months for 5 years and then annually, as well as yearly diagnostic mammography.

The vast majority of recurrences of DCIS are in-breast recurrences following breast conserving therapy, and most recurrences occur close to the site of prior disease. In those women for whom the initial DCIS was treated with excision alone, the treatment decision making for a recurrence of DCIS is similar to that followed previously. .In those women for whom the initial DCIS was treated with breast conserving surgery plus radiation therapy, mastectomy is usually necessary following a recurrence of DCIS. Local recurrences following

mastectomy for DCIS should be treated with wide local excision with consideration for chest wall irradiation.

Overall, approximately half of the local recurrences following initial treatment for a pure DCIS are again DCIS, and the others are invasive cancer. Those with local recurrences that are invasive should receive systemic treatment as appropriate for a newly diagnosed invasive breast cancer.

Stage I, IIA, IIB, or T3N1M0 Invasive Breast Cancer

The recommended work-up and staging of invasive breast cancer includes: history and physical exam; a complete blood cell count; platelet count; liver function tests**;** bilateral diagnostic mammography; breast ultrasonography, if necessary; tumor ER and PR determinations; HER2 tumor status determination; and pathology review (see BINV-1). Genetic counseling is recommended if the patient is considered to be at high risk of hereditary breast cancer as defined by the NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Guidelines.

Use of MRI to evaluate women considering breast-conserving therapy is optional. If MRI imaging of the breast is performed, it should be done with a dedicated breast coil, with consultation with the multidisciplinary treatment team, and by a breast imaging team capable of performing MRI-guided biopsy (see BINV-B). The limitations of breast MRI include a high percentage of false-positive findings.[39-41] MRI imaging of the breast, therefore, should generally be considered in the staging of breast cancer for patients whose breasts cannot be imaged adequately with mammography and ultrasound (eg, women with very dense breast tissue, women with positive axillary nodal status and occult primary tumor presumed to originate in the breast, or to evaluate the chest wall). No randomized, prospective assessment of the utility of MRI in the staging or treatment decision making in breast cancer treatment are available. One retrospective study suggested an outcome benefit[42] whereas another did not.[43] One systematic review[41] documented breast MRI staging to alter surgical treatment in 7.8% to 33.3% of women.[41] However, no differences in outcome, if any, can be demonstrated in that analysis. Patients should not be denied the option of breast conservation therapy based upon MRI findings alone in the absence of tissue sampling.

Additional staging studies involving bone scan or abdominal imaging using CT, ultrasound, or MRI are optional. These studies are not indicated in patients with stage I disease without signs/symptoms of metastatic disease, nor are they needed in many other patients with early-stage breast cancer.[44] Radionuclide bone scanning and abdominal imaging with CT, ultrasound, or MRI are typically indicated only for patients with signs or symptoms related to bone or abdomen (eg, bone scan if alkaline phosphatase is elevated, abdominal scan if liver function tests are abnormal) or in T3N1M0 disease (category 2B for bone scan in T3N1M0 disease). These recommendations are supported by a study evaluating patients with newly diagnosed breast cancer by bone scan, liver ultrasonography, and chest radiography.[45] Metastases were identified by bone scan in 5.1%, 5.6% and 14% of patients with stage I, II and III disease, respectively, and no evidence of metastasis was detected by liver ultrasonography or chest radiography in patients with stage I or II disease.

The panel recommends against the use of positron emission tomography (PET) or PET/CT scanning in the staging of these patients. The recommendation against the use of PET scanning is because of the high false negative rate in the detection of lesions that are small (< 1 cm) and/or low grade, the relatively low sensitivity for detection of axillary nodal metastases, the low prior probability of the patients having detectable metastatic disease, and the high rate of false-positive scans.[46-51]

Along with ER- and PR-, the determination of HER2 status for all newly diagnosed invasive breast cancers is specified in the guidelines. HER2 status can be assessed by measuring the number of HER2 gene copies (fluorescence in situ hybridization [FISH]), or by a complementary method in which the quantity of HER2 cell surface receptors is assessed (immunohistochemistry [IHC]).[52] Five methods currently have United States Food and Drug Administration approval for determining the HER2 status of breast cancer tumors. These methods include: 1) the IHC HercepTest® (DAKO, Glostrup, Denmark)[53]; 2) the IHC Pathway® HER2 test (Ventana Medical Systems, Tucson, AZ)[54]; 3) the INFORM® HER2 FISH test (Ventana Medical Systems)[55]; 4) the PathVysion® HER2 FISH test (Vysis, Downers Grove, IL)[56]; 5) and the SPOT-Light® HER2 CISH test (Invitrogen, Carmarillo, CA) [57] although modifications of these methods are currently in use in many anatomic pathology laboratories. The accuracy of HER2 assays used in clinical practice is a major concern, and results from several studies have shown that false-positive[58-62] as well as false-negative[58,63] HER2 test results are common. An NCCN Task Force has reviewed this topic and issued recommendations on HER2 testing in breast cancer[64] which are summarized in the guideline (see BINV-A). The Panel considers either an IHC or FISH test as an acceptable method for making an initial determination of HER2 tumor status provided that the test method has been validated and shown to be at least 95% concordant with another validated method. Evidence for 95% concordance between the HER2 assay used and a validated complementary HER2 testing method is also required. Breast cancer tumors are classified as HER2-positive if they demonstrate HER2 gene amplification by a FISH method or are scored as 3+ by an IHC method. Strategies for evaluating tumors with borderline or indeterminate HER2 status (eg, FISH [Pathvysion®] scores of 1.8-2.2 HER2 genes/chromosome 17/cell, FISH [INFORM®] scores of greater than 4 to less than 6 HER2 genes/cell, or 2+ scores by IHC) are described in the guideline (see BINV-A). HER2 testing should be performed only in laboratories accredited to carry out such testing. Further, these laboratories should have standardized HER2 testing procedures in place, as well as programs to periodically evaluate the proficiency of personnel performing HER2 testing. HER2 test reports must provide information on site of tumor; specimen type; histologic type; fixation method and time; block examined; HER2 testing method used; results of ongoing validation and concordance studies of the HER2 testing methods used in that laboratory, as well as other laboratory quality assurance information. Clinicians should be familiar with the significance of these criteria when making clinical recommendations for an individual patient.

A joint panel from ASCO and CAP has recently issued HER2 testing guidelines which are fully consistent with those recommended by NCCN, but which also provide detailed recommendations for a substantial ongoing quality assurance program for laboratory accreditation from CAP.[65] The Panel endorses CAP accreditation for anatomic pathology laboratories performing HER2 testing.

A determination of the HER2 status of the tumor is recommended for prognostic purposes for patients with node-negative breast cancer.[66] HER2 tumor status also provides baseline predictive information used in selecting optimal adjuvant/neoadjuvant therapy and in the selection of therapy for recurrent or metastatic disease (category 1). For example, retrospective analyses have demonstrated that anthracycline-based adjuvant therapy is superior to non-anthracycline-based adjuvant chemotherapy in patients with HER2-positive tumors,[67-71] and that the dose of doxorubicin may be important in the treatment of tumors that are HER2-positive.[72] However, prospective evidence of the predictive utility of HER2 status in early-stage[73-76] and metastatic breast cancer[77-79] is currently available only for trastuzumab-containing therapies.

ER- and PR- tumor status is normally determined by IHC testing. Although this method is considered reliable when performed by experienced pathology personnel, there have been a number of reports

indicating that the reliability of ER and PR determinations can vary widely from one laboratory to another.[80-82] These inter-laboratory differences may be attributable to the diverse methodologies and diverse interpretation schema used to evaluate tumor hormonal status.

Local-regional treatment

A number of randomized trials document that mastectomy with axillary lymph node dissection is equivalent to breast-conserving therapy with lumpectomy, axillary dissection, and whole breast irradiation, as primary breast treatment for the majority of women with stage I and stage II breast cancers (category 1).[83-86] When breast-conserving therapy with lumpectomy and radiation therapy is performed, the Panel finds the data inadequate to support the use of partial breast irradiation outside the confines of a high-quality, prospective clinical trial.[87] The Panel recommends whole breast irradiation to include the majority of the breast tissue; breast irradiation should be performed following CT-based treatment planning so as to limit irradiation exposure of the heart and lungs, and to assure adequate coverage of the primary tumor and surgical site. Tissue wedging, forward planning with segments (step and shoot), or intensity-modulated radiation therapy (IMRT) is recommended.[88] Dose/fraction schedules of either 50 Gy in 25 fractions over 35 days or 42.5 Gy in 16 fractions over 22 days have been prospectively evaluated and are comparable with respect to DFS and overall survival in a study of women with node-negative early-stage breast cancer with a median follow-up of 69 months.[89] Randomized trials have demonstrated a decrease in in-breast recurrences with an additional "boost" dose of radiation (by photons, brachytherapy, or electron beam) to the tumor bed.[90,91] The relative reduction in risk of local recurrence with the addition of a "boost" is similar across age groups (from ≤ 40 years to > 60 years) while the absolute gain in local control is highest in the younger patients. There is a demonstrated benefit favoring a boost in patients with positive axillary nodes, lymphovascular invasion, or close margins. (See BINV-H [Principles of Radiation Therapy]). For example, a subset analysis from an EORTC trial including only those patients (1724 patients out of 5318 total) for whom central pathology review of tumor margins was available demonstrated that the 10-year relapse rate was significantly lower when women with positive tumor margins received a "boost" (4% vs. 13%; P=0.0001). However, a "boost" did not significantly lower the relapse rate in the group with negative margins.[92] Hence, the Panel recommends consideration of a "boost" after post-lumpectomy whole breast irradiation (see BINV-2).

The use of breast-conserving therapy is absolutely contraindicated for patients who have received previous moderate- or high-dose radiation to the breast or chest wall, are pregnant and would require radiation during pregnancy, have diffuse suspicious or malignant-appearing microcalcifications on mammography, have widespread disease that cannot be incorporated by local excision through a single incision with a satisfactory cosmetic result, or have positive pathologic margins (see BINV-E; BINV-F). Patients with a pathologically positive margin should generally undergo re-excision(s) to achieve a negative pathologic margin. If the margins remain positive after re-excision(s), then mastectomy is required for optimal local disease control. In order to adequately assess margins following lumpectomy, the Panel recommends that the surgical specimens be oriented, that the pathologist provide descriptions of the gross and microscopic margin status, and the distance, orientation, and type of tumor (invasive or DCIS) in relation to the closest margin.

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

Several studies of women with early-stage breast cancer treated with breast-conserving therapy have identified young age as a significant predictor of an increased likelihood of ipsilateral breast tumor recurrence after breast conserving surgery or mastectomy.[93-95] Risk factors, such as a family history of breast cancer or a genetic predisposition for breast cancer (eg, *BRCA 1/2* or other mutation), are more likely to exist in the population of young women with breast cancer, thereby confounding the independent contributions of age and treatment to clinical outcome.[96] Survival outcomes for young women with breast cancer receiving either breast-conserving therapy or mastectomy are similar.[97] The Panel recommends that women with breast cancer who are ≤35 years or premenopausal and carriers of a known *BRCA 1/2* mutation consider additional risk reduction strategies (see BINV-F; NCCN Breast Risk Reduction Guidelines and NCCN Genetic/Familial High-Risk Assessment Guidelines)

Whole breast irradiation as a component of breast conserving therapy is not always necessary in selected women 70 years of age or older. In a study of women with clinical stage I, ER-positive breast cancer, who were 70 years of age or older at diagnosis, patients were randomized to receive lumpectomy with whole breast radiation or lumpectomy alone, both with tamoxifen for 5 years. Local-regional recurrence rates were 1% in the lumpectomy, radiation and tamoxifen arm, and 4% in the lumpectomy plus tamoxifen arm. There were no differences in overall survival, disease-free survival or need for mastectomy.[98] These results were confirmed in an updated analysis of this study with a median follow-up of 8.2 years.[99] Similar results were obtained in another study of similar design.[100] The Guidelines allow for the use of breast-conserving surgery (pathologically negative margin required) plus tamoxifen or an aromatase inhibitor without breast irradiation in women age 70 or older with clinically negative lymph nodes and ER positive breast cancer (category 1 with tamoxifen; category 2A with an aromatase inhibitor).

If adjuvant chemotherapy is indicated following breast-conserving surgery, radiation should typically be given after chemotherapy is completed.[101] Breast-conserving radiation therapy may be given concurrent with CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy, but methotrexate should either be withheld during the radiation or limited to no more than 2 doses concurrent with the radiation. Concurrent CMF chemotherapy with radiation has been demonstrated to decrease the cosmetic outcome of breast-conserving therapy in some, but not all studies.[102-104] The guideline includes a recommendation for regional lymph node irradiation in patients treated with breast-conserving surgery (see BINV-2) in situations analogous to those recommended for patients treated with post-mastectomy regional lymph node irradiation (see BINV-3; subsequent discussion; Principles of Radiation [BINV-H]).

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

Performance of sentinel lymph node mapping and resection in the surgical staging of the axilla is recommended by the Panel as the preferred method to assess the pathologic status of the axillary lymph nodes for patients with stage I or stage II breast cancer[35,105-112] (see BINV-C). This recommendation is supported by results of recent randomized clinical trials showing decreased arm and shoulder morbidity (eg, pain, lymphedema, and sensory loss) in patients with breast cancer undergoing sentinel lymph node biopsy compared with patients undergoing standard axillary node dissection.[111,113] No significant differences in the effectiveness of the sentinel lymph node procedure or level I and II dissection in determining the presence or absence of metastases in axillary nodes were seen in these studies. However, not all women are candidates for sentinel lymph node

resection. The availability of an experienced sentinel lymph node team is mandatory for the use of sentinel lymph node mapping and excision.[114, 115] Women who have clinical stage I or II disease and do not have immediate access to an experienced sentinel node team should be considered for referral to an experienced sentinel lymph node team for the definitive surgical treatment of the breast and surgical axillary lymph node staging. In addition, potential candidates for sentinel lymph node mapping and excision should have clinically negative axillary lymph nodes, or a negative core or fine needle aspiration (FNA) biopsy of any clinically suspicious axillary lymph node(s). If the sentinel lymph node cannot be identified or is positive for metastasis, a formal axillary lymph node dissection should be performed (category 2A) or axillary irradiation administered (category 2B). The optimal technique for axillary radiation is not established in studies, but the axillary nodes can be included in the breast tangential fields. If lymph node mapping identifies sentinel lymph nodes in the internal mammary chain, internal mammary node excision is considered optional (category 3). In many institutions, sentinel lymph nodes are assessed for the presence of metastases by both H&E staining and cytokeratin IHC. The clinical significance of a lymph node that is negative by H&E staining but positive by cytokeratin IHC is not clear. Because the historical and clinical trial data on which treatment decisions are based have relied on H&E staining, the Panel believes that current treatment decisions should be made based solely on H&E staining (category 3). In the uncommon situation in which H&E staining is equivocal, reliance on the results of cytokeratin IHC is reasonable.

Level I or II axillary dissection is an appropriate staging study in women with invasive breast cancer. Although the option of sentinel lymph node mapping and excision is preferred by the Panel over axillary lymph node dissection as the initial axillary lymph node staging for women with clinically node-negative stage I or stage II breast cancer, it is not a mandatory replacement for a level I and II axillary dissection. Axillary lymph node dissection remains indicated in women found to have axillary lymph node involvement on sentinel lymph node excision. Traditional level I and level II axillary dissection required that at least 10 lymph nodes should be provided for pathologic evaluation to accurately stage the axilla.[116,117] Axillary dissection should be extended to include level III nodes only if gross disease is apparent in the level I or II nodes.

Furthermore, in the absence of definitive data demonstrating superior survival with axillary lymph node dissection or sentinel lymph node resection, these procedures may be considered optional in patients who have particularly favorable tumors, patients for whom the selection of adjuvant systemic therapy is unlikely to be affected by the results of the procedure, elderly patients, and patients with serious co-morbid conditions (see BINV-D). Women who do not undergo axillary dissection or axillary lymph node irradiation are at increased risk for ipsilateral lymph node recurrence.[118] Women who undergo mastectomy are appropriate candidates for breast reconstruction.

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

Preoperative chemotherapy should be considered for women with large clinical stage IIA, stage IIB, and T3N1M0 tumors who meet the criteria for breast-conserving therapy except for tumor size and who wish to undergo breast-conserving therapy. In the available clinical trials of preoperative chemotherapy, pretreatment biopsies have been limited to core needle biopsy or FNA cytology. Therefore, in patients anticipated to receive preoperative chemotherapy, core biopsy of the breast tumor and localization of the tumor bed for future surgical management should be performed. For patients with clinically negative axillary nodes, sentinel lymph node biopsy can be considered. For those with clinically suspicious axillary lymph nodes, the Panel recommends consideration of either a core biopsy or FNA of these nodes, along with a sentinel node biopsy if biopsy results are negative.[119] Preoperative

chemotherapy is not indicated unless invasive breast cancer is confirmed. Recommended staging studies are outlined on BINV-10 and include history and physical examination, CBC, platelet count, liver function tests, diagnostic bilateral mammogram (with ultrasound as necessary), pathology review, and determination of tumor ER/PR and HER2 status. Breast MRI, bone scan, and abdominal imaging are optional unless the patient is symptomatic or as directed based upon other abnormal or suspicious staging evaluations; chest imaging is recommended if pulmonary symptoms are present.

The current guideline lists pre-chemotherapy sentinel lymph node resection as the preferred option for surgical axillary staging in those women with clinically negative ipsilateral axillary examinations (see BINV-C). If the sentinel lymph node is histologically negative, omission of the axillary dissection may be considered at the time of local, surgical therapy. If the sentinel lymph node is histologically positive, then level I and II axillary dissection should be performed at the time of definitive surgical therapy. If a pre-chemotherapy sentinel lymph node excision is not performed, then a level I and II axillary dissection (category 2A) or sentinel lymph node excision (category 3) (with level I and II axillary dissection if sentinel lymph node is positive) should be performed at the time of definitive surgical therapy. The Panel generally recommends a pre-chemotherapy sentinel lymph node excision because it provides additional information to guide local and systemic treatment decisions. In the event that sentinel lymph node resection is performed after administration of preoperative chemotherapy, both the pre-chemotherapy clinical and the post-chemotherapy pathologic nodal stages must be used to determine the risk of local recurrence. Close communication between members of the multidisciplinary team, including the pathologist, is particularly important when any treatment strategy involving preoperative chemotherapy is planned.

In some patients, preoperative chemotherapy results in sufficient tumor response that breast-conserving therapy becomes possible. Because complete or near-complete clinical responses are common, the use of percutaneously placed clips into the breast under mammographic or ultrasound guidance or other method of localizing pre-chemotherapy tumor volume aids in the post-chemotherapy resection of the original area of tumor and is encouraged. The results of the NSABP B-18 trial show that breast conservation rates are higher after preoperative chemotherapy.[120] However, preoperative chemotherapy has no demonstrated disease specific survival advantage over postoperative adjuvant chemotherapy in patients with stage II tumors. NSABP B-27 is a 3-arm, randomized phase III trial of women with invasive breast cancer treated with preoperative doxorubicin and cyclophosphamide (AC) chemotherapy for 4 cycles followed by local therapy alone, preoperative AC followed by preoperative docetaxel for 4 cycles followed by local therapy, or AC followed by local therapy followed by 4 cycles of postoperative docetaxel. Results from this study which involved 2411 women documented a higher rate of complete pathologic response at the time of local therapy in patients treated preoperatively with 4 cycles of AC followed by 4 cycles of docetaxel versus 4 cycles of preoperative AC. Disease-free survival and overall survival have not been shown to be superior following docetaxel treatment in B-27.[121] A disease-free survival advantage was observed (hazard ratio 0.71; 95% CI, 0.55 – 0.91; P=0.007) favoring preoperative versus postoperative docetaxel in the subset of patients experiencing a clinical partial response to AC.

A number of chemotherapy regimens have been studied as preoperative chemotherapy in the neoadjuvant setting. The Panel believes that the regimens recommended in the adjuvant setting (see BINV-J) are appropriate to consider in the preoperative chemotherapy setting. In women with HER2-positive tumors treated with neoadjuvant chemotherapy, the addition of neoadjuvant trastuzumab to paclitaxel

followed by FEC chemotherapy was associated with an increase in the pathologic complete response rate from 26% to 65.2% (P=0.016).[122] Thus, the incorporation of trastuzumab into neoadjuvant chemotherapy regimens appears important in HER2-positive tumors.

Several randomized trials have assessed the value of neoadjuvant endocrine therapy in postmenopausal women with ER-positive breast cancer. These studies have generally compared the rates of objective response and rates of breast-conserving surgery among treatment with tamoxifen, anastrozole, anastrozole plus tamoxifen, or letrozole. These studies consistently demonstrate that the use of either anastrozole or letrozole alone provides superior rates of breast-conserving surgery and usually objective response.[123,124] On the basis of these trials, preoperative endocrine therapy with an aromatase inhibitor is an option in the treatment of postmenopausal women with hormone receptor-positive disease.

If the tumor responds to preoperative chemotherapy, lumpectomy plus (if pre-chemotherapy sentinel lymph node staging was not done or was positive) axillary lymph node dissection (category 2A) or (if pre-chemotherapy axillary lymph node staging not performed) sentinel lymph node procedure (category 3) may be considered if the requirements for breast-conserving therapy are fulfilled (see BINV-11; BINV-12). If a pre-chemotherapy sentinel lymph node procedure was performed and the sentinel lymph node was pathologically negative, then further axillary lymph node staging is not necessary. If a pre-chemotherapy sentinel lymph node procedure was performed and the sentinel lymph node was positive, then a level I/II axillary lymph node dissection should be performed. Surgery should be followed by individualized chemotherapy such as taxanes (category 2B) if the full course of planned chemotherapy was not administered preoperatively, as well as breast and regional lymph node irradiation. The consensus of the Panel is that there is no role for postoperative chemotherapy if a full course of standard chemotherapy has been completed preoperatively. If after several cycles of preoperative chemotherapy, the tumor fails to respond, the response is minimal, or if the disease progresses at any point, an alternative chemotherapy should be considered, followed by local therapy, usually a mastectomy plus axillary dissection, with or without breast reconstruction. Postoperative treatment for these patients consists of individualized chemotherapy, and endocrine therapy in women with ER- and/or PR-positive tumors. Up to one year of trastuzumab therapy should be completed if tumor is HER2-positive (category 1). Radiation should be delivered to the chest wall and supraclavicular lymph nodes (see Principles of Radiation Therapy [BINV-H]). Inclusion of the internal mammary lymph nodes in the radiation therapy field can be considered, but this recommendation generated substantial controversy among Panel members (category 3). Postmastectomy radiation therapy in patients with T2N0M0 tumors may be considered optional. Capecitabine can be administered as a radiation sensitizer for patients at high risk of local recurrence (category 2B). Endocrine therapy and trastuzumab can be administered concurrent with radiation therapy if indicated. If capecitabine is administered as a radiation sensitizer, trastuzumab may be given concurrently.

Radiation therapy after mastectomy

Node positive disease

Three randomized clinical trials have shown that a disease-free and overall survival advantage is conferred by the addition of chest wall and regional lymph node irradiation in women with positive axillary lymph nodes after mastectomy and axillary lymph node dissection.[125-129] In these trials, not only the ipsilateral chest wall but also the ipsilateral local-regional lymph nodes were irradiated. These studies contrast, however, with a number of other studies, including a randomized trial from an NCCN institution that failed to show a survival advantage with

postmastectomy chest wall and regional node irradiation.[130] However, on the basis of the studies demonstrating a survival advantage with postmastectomy chest wall and regional lymph node irradiation in node-positive breast cancer, the current Guidelines call for postmastectomy irradiation in women with 4 or more positive axillary lymph nodes and strong consideration of postmastectomy irradiation in women with 1-3 positive axillary lymph nodes. Two retrospective analyses have provided some evidence for benefit of radiation therapy for only selected patients receiving preoperative chemotherapy prior to mastectomy.[131,132] However, the Panel recommends that decisions related to administration of radiation therapy for patients receiving neoadjuvant chemotherapy should be made on the basis of pre-chemotherapy tumor characteristics, irrespective of tumor response to preoperative chemotherapy (ie, RT is recommended in patients with clinical stage III disease and a pathologic complete response to neoadjuvant chemotherapy).

For women with 1 to 3 involved axillary lymph nodes, the Panel recommends strong consideration of radiation to the chest wall and supraclavicular area after chemotherapy (category 1), with consideration also given to the inclusion of the ipsilateral internal mammary nodal field (category 3). The recommendation for chest wall and supraclavicular irradiation in women with 1-3 involved axillary lymph nodes generated substantial controversy among Panel members. The use of regional nodal irradiation is supported by a subgroup analysis of studies from the Danish Breast Cancer Collaborative Group.[133] In this analysis, a substantial survival benefit was associated with postmastectomy radiation therapy for women with 1-3 positive axillary lymph nodes. Some Panel members believe chest wall and supraclavicular irradiation should be used routinely after mastectomy and chemotherapy in this subgroup of patients. However, other Panel members believe radiation should be considered in this setting but should not be mandatory given the studies that do not show an advantage. This is an unusual situation in which high-level evidence (category 1) exists but is contradictory.[84,126,127,129,133] Women with 1 to 3 involved axillary lymph nodes and with tumors greater than 5 cm or tumors with positive pathologic margins postmastectomy should receive post-chemotherapy radiation therapy to the chest wall and supraclavicular areas (category 1) with consideration of inclusion of the ipsilateral internal mammary field (category 3).

There is considerable disagreement regarding the inclusion of the ipsilateral internal mammary field. Some Panel members believe that irradiation of the internal mammary nodes is unnecessary and produces possible morbidity. Internal mammary node radiation has not been isolated as an independent factor in decreasing recurrence. Others believe internal mammary nodes should be included in the radiation fields, as used in the studies that demonstrated an advantage for postmastectomy, post-chemotherapy radiation therapy. Therefore, this recommendation is identified as category 3.

Women with 4 or more positive axillary lymph nodes are at substantially increased risk for locoregional recurrence of disease. The use of postmastectomy, post-chemotherapy chest wall and regional lymph node irradiation is recommended (category 1). The use of prophylactic chest wall irradiation in this setting substantially reduces the risk of local recurrence.[84] Again, there was substantial disagreement among Panel members regarding the inclusion of the ipsilateral internal mammary field (category 3).

Postmastectomy irradiation should be performed using CT-based treatment planning to assure reduced radiation dose to the heart and lungs. The recommended radiation is 50 Gy in fractions of 1.8-2.0 Gy to the ipsilateral chest wall, mastectomy scar, and drain sites. Additional “boost” dose of radiation to the mastectomy scar can be delivered (eg, 2 Gy fractionated in 5 doses, typically with electrons).

Radiation dose to regional lymph nodes is 50 Gy given using 1.8-2.0 Gy fraction size.

Node negative disease

Features in node-negative tumors that predict a high rate of local recurrence include primary tumors greater than 5 cm and close (less than 1 mm) or positive pathologic margins. Chest wall irradiation is recommended for these patients.[134] Consideration should be given to radiation to the ipsilateral supraclavicular area (category 2B) and to the ipsilateral internal mammary lymph nodes (category 3), especially in patients with inadequate axillary evaluation or extensive lymphovascular invasion. Postmastectomy radiation therapy is not recommended for patients with negative margins, tumors 5 cm or smaller, and no positive axillary lymph nodes. The Panel recommends that decisions related to administration of radiation therapy for patients receiving preoperative chemotherapy should be made on the basis of pre-chemotherapy tumor characteristics irrespective of response to neoadjuvant chemotherapy.

Breast reconstruction

Breast reconstruction following mastectomy

A number of factors must be considered in the decision-making about breast reconstruction following mastectomy (see BINV-G). First, there are a number of different types of breast reconstruction. These include reconstruction using implants, autologous tissue, or both implants and autologous tissue. Implant reconstruction typically involves the placement of a sub-pectoralis major expander implant, a series of expansions, followed by replacement of the expander with a permanent sub-pectoralis major implant. A number of different techniques are available for the performance of autologous reconstruction using various combinations of muscle, fat and skin from a variety of donor sites. The decision regarding type of reconstruction includes patient preference, body habitus, smoking history, comorbidities, plans for irradiation, and expertise and experience of the reconstruction team. For many patients, reconstruction may be performed as an immediate procedure under the same anesthetic as the mastectomy. Reconstruction is an optional procedure that does not impact the probability of recurrence or death, but it is associated with an improved quality of life for many patients.

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

Breast reconstruction following breast conserving surgery

Issues related to breast reconstruction also pertain to women who undergo or have undergone a lumpectomy, particularly in situations where the surgical defect is large and/or expected to be cosmetically unsatisfactory. The evolving field of oncoplastic surgery includes the use of “volume displacement” techniques performed in conjunction with a large partial mastectomy.[135] Oncoplastic volume-displacement procedures combine the removal of generous regions of breast tissue (typically designed to conform to the segmentally distributed cancer in the breast) with “mastopexy” techniques in which remaining breast tissues are shifted together within the breast envelope to fill the resulting surgical defect and thereby avoid the creation of significant breast deformity. Volume displacement techniques are generally performed during the same operative setting as the breast conserving lumpectomy by the same surgeon who is performing the cancer resection.[136,137]

Advantages of oncoplastic volume displacement techniques are that they permit the removal of larger regions of breast tissue, thereby achieving wider surgical margins around the cancer, at the same time that they better preserve the natural shape and appearance of the

breast than do standard breast resections.[138] Limitations of oncoplastic volume displacement techniques include lack of standardization among centers, performance at only a limited number of sites in the U.S, and the possible necessity for subsequent mastectomy if pathologic margins are positive when further breast conserving attempts are deemed impractical or unrealistic. Nevertheless, the consensus of the Panel is that these issues should be considered prior to surgery for women who are likely to have a surgical defect that is cosmetically unsatisfactory, and that women who undergo lumpectomy and are dissatisfied with the cosmetic outcome after treatment should be offered a consultation with a plastic surgeon to address the repair of resulting breast defects. Finally, it is important to note that the primary focus should be on treatment of the tumor, and such treatment should not be compromised when decisions regarding breast reconstruction are made.

Systemic adjuvant therapy

After surgical treatment, adjuvant systemic therapy should be considered. The published results of the Early Breast Cancer Trialists' Collaborative Group overview analyses of adjuvant polychemotherapy and tamoxifen show convincing reductions in the odds of recurrence and of death in all age groups under 70 years for polychemotherapy and in all age groups for tamoxifen.[2] Thus, for those under age 70, the current Guidelines recommend adjuvant therapy without regard to patient age (category 1). The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of the therapy and comorbidity.[139,140] The decision-making process requires a collaboration involving the health care team and the patient.

Estimating risk of relapse or death and benefits of systemic treatment

A number of prognostic factors predict for future recurrence or death from breast cancer. The strongest prognostic factors are patient age, comorbidity, tumor size, tumor grade, number of involved axillary lymph nodes, and possibly HER2 tumor status. Algorithms have been published estimating rates of recurrence,[139] and a validated computer-based model (Adjuvant! Online; www.adjuvantonline.com) is available to estimate 10-year disease-free and overall survival that incorporates all of the above prognostic factors except for HER2 tumor status.[140,141] These tools aid the clinician in objectively estimating outcome with local treatment only, and also assist in estimating the absolute benefits expected from systemic adjuvant endocrine therapy and chemotherapy. These estimates may be utilized by the clinician and patient in their shared decision-making regarding the toxicities, costs, and benefits of systemic adjuvant therapy.[142]

Use of DNA microarray technologies to characterize breast cancer has allowed the development of classification systems of breast cancer by gene expression profile.[143] Five major subtypes of breast cancer have been identified by DNA microarray gene expression profiling: ER-positive/HER2-negative (Luminal A and Luminal B subtypes); ER-negative/HER2-negative (Basal subtype); HER2-positive; and tumors that have characteristics similar to normal breast tissue (Normal breast-like).[144-146] In retrospective analyses, these gene expression subtypes are associated with differing relapse-free and overall survival. A similar approach has been used to define more limited sets of genes for prognostic and predictive purposes.[147] For example, the Mammaprint assay uses microarray technology to analyze a 70-gene expression profile from frozen breast tumor tissue as a means of selecting patients with early-stage, node-negative breast cancer who are more likely to develop distant metastases.[148-150]

Another gene-based approach is the 21-gene assay using reverse transcription polymerase chain reaction (RT-PCR) on RNA isolated from paraffin-embedded breast cancer tissue (Oncotype Dx). On retrospective analysis of two trials (NSABP B-14 and B-20) performed in women with hormone receptor-positive, axillary lymph node-negative invasive breast cancer, this assay system was able to quantify risk of recurrence as a continuous variable (eg, Oncotype Dx recurrence score) and to predict responsiveness to both tamoxifen and CMF or methotrexate/5-fluorouracil/leucovorin chemotherapy.[151,152] A recent comparison of simultaneous analyses of breast cancer tumors using 5 different gene-expression models indicated that 4 of these methods (including Mammaprint and Oncotype Dx) provided similar predictions of clinical outcome.[153]

While many of the DNA microarray technologies are able to stratify patients into prognostic and/or predictive subsets on retrospective analysis, the gene subsets differ from study to study, and prospective clinical trials testing the utility of these techniques have yet to be reported. Currently, 2 prospective randomized clinical trials (TAILORx and MINDACT) are addressing the use of Oncotype DX and MammaPrint, respectively, as predictive and/or prognostic tools in populations of women with early-stage lymph node-negative breast cancer. Pending the results of the prospective trials, the Panel considers the 21-gene RT-PCR assay as an option when evaluating patients with primary tumors characterized as 0.6-1.0 cm with unfavorable features or > 1cm, and node-negative, hormone receptor-positive and HER2-negative (category 2B). In this circumstance, the recurrence score may be determined to assist in estimating likelihood of recurrence and benefit from chemotherapy (category 2B). The Panel emphasizes that the recurrence score should be used for decision-making only in the context of other elements of risk stratification for an individual patient. All recommendations involving use of the recurrence score in treatment decision-making are categorized as 2B (see BINV-6).

Axillary lymph node negative tumors

Small tumors (up to 0.5 cm in greatest diameter) that do not involve the lymph nodes are so favorable that adjuvant systemic therapy is of minimal incremental benefit and is not recommended as treatment of the invasive breast cancer. Tamoxifen may be considered to reduce the risk of a second contralateral breast cancer, especially in those with ER-positive disease. The NSABP database demonstrated a correlation between the ER status of a new contralateral breast tumor and the original primary tumor, which reinforced the notion that tamoxifen is unlikely to be an effective strategy to reduce the risk of contralateral breast cancer in patients diagnosed with ER-negative tumors.[154] Patients with invasive ductal or lobular tumors 0.6 to 1 cm in diameter and no lymph node involvement may be divided into patients with a low risk of recurrence and those with unfavorable prognostic features that warrant consideration of adjuvant therapy. Unfavorable prognostic features include intramammary angiolymphatic invasion, high nuclear grade, high histological grade, HER2-positive status, or hormone receptor-negative status (category 2B). The use of endocrine therapy and chemotherapy in these relatively lower risk subsets of women must be based on balancing the expected absolute risk reduction and the individual patient's willingness to experience toxicity to achieve that incremental risk reduction.

Patients with lymph node involvement or with tumors greater than 1 cm in diameter are appropriate candidates for adjuvant systemic therapy (category 1). For women with lymph node-negative, hormone receptor-negative tumors greater than 1 cm in diameter, chemotherapy is recommended (category 1). For those with lymph node-negative, hormone receptor-positive breast cancer tumors greater than 1 cm, endocrine therapy with chemotherapy is recommended (category 1).

The incremental benefit of combination chemotherapy in patients with lymph node-negative, hormone receptor-positive breast cancer may be relatively small.[155] Therefore, the Panel recommends that tumor hormone receptor status be included as one of the factors considered when making chemotherapy-related treatment decisions for patients with node-negative, hormone receptor-positive breast cancer. Patients for whom this evaluation may be especially important are those with tumors characterized as 0.6-1.0 cm and hormone receptor-positive with unfavorable features, or greater than 1 cm and hormone receptor-positive and HER2-negative (see BINV-5; BINV-6). However, chemotherapy should not be withheld from these patients solely on the basis of ER-positive tumor status.[2,155,156]

The use of genomic/gene expression array data which also incorporate additional prognostic/predictive biomarkers (eg, Oncotype Dx recurrence score) may provide additional prognostic and predictive information beyond anatomic staging and determination of ER/PR and HER2 status. Assessment of the role of the genomic/gene expression array technology is difficult because of the retrospective nature of the studies, the evolution of chemotherapy and hormone therapy regimens, and the overall more favorable prognosis of the patients with lymph node-negative disease compared with those enrolled in the historically-controlled clinical trials. Some NCCN institutions consider performing RT-PCR analysis (eg, Oncotype DX assay) to further refine risk stratification for adjuvant chemotherapy for patients with node-negative, ER-positive, HER2-negative breast cancers greater than 0.5 cm, whereas others do not (category 2B).

Axillary lymph node positive tumors

Patients with lymph node-positive disease are candidates for chemotherapy and, if the tumor is hormone receptor-positive, for the addition of endocrine therapy (category 1). In postmenopausal women, with hormone receptor-positive disease, an aromatase inhibitor should be utilized either as initial adjuvant therapy, sequential with tamoxifen, or as extended therapy following tamoxifen. In premenopausal women, adjuvant tamoxifen is preferred. If both chemotherapy and tamoxifen are used, data from the Intergroup trial 0100 suggest that delaying initiation of tamoxifen until after completion of chemotherapy improves disease-free survival compared with concomitant administration.[156] Consequently, chemotherapy followed by endocrine therapy should be the preferred therapy sequence.

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

Guideline stratification for systemic adjuvant therapy

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

Adjuvant endocrine therapy

The NCCN Guidelines call for the determination of ER and PR content in all primary invasive breast cancers. Patients with invasive breast cancers that are ER- or PR-positive should be considered for adjuvant endocrine therapy regardless of patient age, lymph node status, or whether or not adjuvant chemotherapy is to be administered.[157] Selected studies suggest that HER2-positive breast cancers may be less sensitive to some endocrine therapies, although other studies have failed to confirm this finding.[69,158-165] A retrospective analysis of tumor blocks collected in the Arimidex, Tamoxifen, Alone or in Combination

(ATAC) Trial indicated that HER2 amplification is a marker of relative endocrine resistance independent of type of endocrine therapy.[166] However, given the favorable toxicity profile of the available endocrine therapies, the Panel recommends the use of adjuvant endocrine therapy in the majority of women with hormone receptor-positive breast cancer regardless of menopausal status, age, or HER2 status of the tumor. The exceptions to the recommendation of adjuvant endocrine therapy for patients with hormone receptor-positive disease are those patients with lymph node-negative cancers less than or equal to 0.5 cm or 0.6 to 1.0 cm in diameter with favorable prognostic features where the prognosis is so favorable that the benefits of adjuvant endocrine therapy are very small.

The most firmly established adjuvant endocrine therapy is tamoxifen for both premenopausal and postmenopausal women.[2] In women with ER-positive breast cancer, adjuvant tamoxifen decreases the annual odds of recurrence by 39% and the annual odds of death by 31% irrespective of the use of chemotherapy, patient age, menopausal status, or axillary lymph node status.[2] Prospective, randomized trials demonstrate that the optimal duration of tamoxifen appears to be five years. In patients receiving both tamoxifen and chemotherapy, chemotherapy should be given first, followed by sequential tamoxifen.[156]

A number of studies have evaluated aromatase inhibitors in the treatment of postmenopausal women with early-stage breast cancer. These studies have utilized the aromatase inhibitors as initial adjuvant therapy, as sequential therapy following 2-3 years of tamoxifen, or as extended therapy following 4.5 -6 years of tamoxifen. The aromatase inhibitors are not active in the treatment of women with functioning ovaries and should not be used in women whose ovarian function cannot be reliably assessed owing to treatment-induced amenorrhea (see Definition of Menopause, BINV-K). The results from two prospective, randomized clinical trials have provided evidence of an overall survival benefit for patients with early-stage breast cancer receiving initial endocrine therapy with tamoxifen followed sequentially by anastrozole (hazard ratio 0.53; 95% CI, 0.28-0.99; P=0.045) or exemestane (hazard ratio 0.83; 95% CI, 0.69-1.00; P=0.05 [excluding patients with ER-negative disease]) when compared with tamoxifen as the only endocrine therapy.[167,168] In addition, the National Cancer Institute Canada Clinical Trials Group (NCIC CTG) MA-17 trial demonstrated a survival advantage with extended therapy with letrozole compared with placebo in women with axillary lymph node-positive (but not lymph node-negative), ER-positive breast cancer.[169] However, no survival differences have been reported for patients receiving initial adjuvant therapy with an aromatase inhibitor versus first-line tamoxifen.[170,171] Tamoxifen and aromatase inhibitors have different side effect profiles. Both contribute to hot flashes, night sweats and may cause vaginal dryness. Aromatase inhibitors are more commonly associated with musculoskeletal symptoms, osteoporosis, and increased rate of bone fracture, while tamoxifen is associated with an increased risk of uterine cancer and deep venous thrombosis.

Two studies have examined initial adjuvant endocrine treatment with either tamoxifen or an aromatase inhibitor. The ATAC Trial demonstrated that anastrozole is superior to tamoxifen or the combination of tamoxifen and anastrozole in the adjuvant endocrine therapy of postmenopausal women with hormone receptor-positive breast cancer.[172,173] With a median of 100 months follow-up, results in 5216 postmenopausal women with hormone receptor-positive, early breast cancer enrolled in the ATAC trial demonstrated fewer recurrences (hazard ratio for DFS=0.85; 95% CI, 0.76-0.94; P=0.003) with anastrozole compared with tamoxifen.[170] No difference in survival has been observed (hazard ratio 0.90; 95% CI, 0.75-1.07; P=0.2). Patients in the combined tamoxifen and anastrozole group gained no benefit over those in the tamoxifen group, suggesting a possible deleterious effect from the weak estrogenic effect of tamoxifen in

patients with near complete elimination of endogenous estrogen levels.[173] ATAC trial sub-protocols show a lesser effect of anastrozole compared with tamoxifen on endometrial tissue,[174] similar effects of anastrozole and tamoxifen on quality of life, with most patients reporting that their overall quality of life was not significantly impaired,[175] a greater loss of bone mineral density with anastrozole,[176] a small pharmacokinetic interference of anastrozole in the presence of tamoxifen of unclear significance,[177] and no evidence for an interaction between prior chemotherapy and anastrozole.[178]

Breast International Group (BIG) 1-98 is a randomized trial testing the use of tamoxifen alone for 5 years, letrozole alone for 5 years, or tamoxifen for 2 years followed sequentially by letrozole for 3 years, or letrozole for 2 years followed sequentially by tamoxifen for 3 years. An early analysis compared tamoxifen alone versus letrozole alone, including those patients in the sequential arms during their first two years of treatment only.[171] With 8,010 women included in the analysis, disease-free survival was superior in the letrozole treated women (hazard rate 0.81; 95% CI 0.70 – 0.93; log rank P=0.003). No interaction between progesterone receptor expression and benefit was observed. No difference in overall survival has been observed. A comparison of the cardiovascular side effects of in the tamoxifen and letrozole arms for of the BIG 1-98 trial showed that the overall incidence of cardiac adverse events was similar (letrozole, 4.8%; tamoxifen, 4.7%). However, the incidence of grade 3 to 5 cardiac adverse events was significantly higher in the letrozole arm, and both the overall incidence and incidence of grade 3 to 5 thromboembolic events was significantly higher in the tamoxifen arm.[179]

Four trials have studied the use of tamoxifen for 2-3 years followed sequentially by a third generation aromatase inhibitor versus continued tamoxifen. The Italian Tamoxifen Anastrozole (ITA) trial randomized 426 postmenopausal women with breast cancer who had completed 2-3 years of tamoxifen to either continue tamoxifen or to switch to anastrozole to complete a total of 5 years of endocrine therapy.[180] The hazard rate for relapse strongly favored sequential treatment with anastrozole (hazard ratio 0.35; 95% CI, 0.18 - 0.68; P=0.001) with a trend towards fewer deaths (P=0.10).[180] Updated results from this study show the hazard ratio for relapse-free survival as 0.56 (95% CI, 0.35-0.89; P=0.01); P value for overall survival analysis remained at 0.1.[181] The Intergroup Exemestane Study (IES) trial randomized 4742 postmenopausal women with breast cancer who had completed a total of 2-3 years of tamoxifen to either continue tamoxifen or to switch to exemestane to complete a total of 5-years of endocrine therapy.[182] The results at a median of 55.7 months of follow-up demonstrated the superiority of sequential exemestane in disease-free survival (hazard ratio 0.76; 95% CI 0.66-0.88; P=0.0001) with a significant difference in overall survival in only patients with ER-positive tumors (hazard ratio 0.83; 95% CI 0.69 - 1.00; log rank P=0.05). A prospectively planned, combined analysis of 3,224 patients enrolled in the Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial 8 and the Arimidex Nolvadex (ARNO 95) trial has also been reported.[183] Patients in this combined analysis had been randomized following 2 years of tamoxifen to complete 5 years of adjuvant tamoxifen or to 3 years of anastrozole. With 28 months median follow-up available, event-free survival was superior with cross-over to anastrozole (hazard ratio 0.60; 95% CI 0.44-0.81; P=0.0009). No statistically significant difference in survival has been observed. An analysis of the ARNO 95 trial alone after 58 months median follow-up demonstrated that switching from tamoxifen to anastrozole was associated with significant increases in both disease-free survival (hazard ratio 0.66; 95% CI, 0.44-1.00; P=0.049) and overall survival (hazard ratio 0.0.53; 95% CI, 0.28-0.99; P=0.045).[168] A meta-analysis of ABCSG 8, ARNO 95 and ITA studies showed significant improvement in overall survival (hazard ratio 0.71, 95% CI, 0.5200.98; P=0.04) with a switch to anastrozole.[184]

Results of the MA-17 trial in 5187 women who had completed 4.5-6 years of adjuvant tamoxifen demonstrated that extended therapy with letrozole provides benefit in postmenopausal women with hormone receptor-positive, early breast cancer.[169,185] At a median follow-up of 2.5 years, the results showed fewer recurrences or new contralateral breast cancers with extended letrozole (hazard ratio 0.58; 95% CI 0.45 - 0.76; P<0.001). No difference in overall survival was demonstrated (hazard rate 0.82; 95% CI 0.57-1.19; P=0.3), although there was a survival advantage in the subset of patients with axillary lymph node-positive disease (hazard rate 0.61; 95% CI 0.38-0.98; P=0.04). In a separate cohort analysis of the MA-17 trial, the efficacy of letrozole versus placebo was evaluated following study unblinding in the 1579 woman who had been randomly assigned to placebo following 4.5-6 years of tamoxifen.[186] The median time since completion of tamoxifen was 2.8 years. Both disease-free survival and distant disease-free survival were found to be significantly improved in the group receiving letrozole, thereby providing some evidence for the efficacy of letrozole in patients who have received 4.5-6 years of tamoxifen therapy followed by no endocrine therapy for an extended period. A formal quality of life analysis demonstrated reasonable preservation of quality of life during extended endocrine therapy, although women may experience ongoing menopausal symptoms and loss of bone mineral density.[187,188]

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

It should be re-emphasized that the aromatase inhibitors are associated with the development of benign ovarian pathology and do not adequately suppress ovarian estrogen synthesis in women with functioning ovaries. Premenopausal women should not be given therapy with an aromatase inhibitor outside the confines of a clinical trial. Women who are premenopausal at the time of diagnosis and who become amenorrheic with chemotherapy may have continued estrogen production from the ovaries in the absence of menses. Serial assessment of circulating LH, FSH, and estradiol to assure a true postmenopausal status is mandatory if this subset of women is to be considered for therapy with an aromatase inhibitor[189,190] (see BINV-K).

Adjuvant cytotoxic chemotherapy

A number of combination chemotherapy regimens are appropriate to consider when adjuvant cytotoxic chemotherapy is utilized (see BINV-J). All adjuvant chemotherapy regimens listed in the guidelines have been evaluated in phase III clinical trials, and the current version of the adjuvant chemotherapy guideline does not distinguish options for chemotherapy regimens by axillary lymph node status. Those regimens

listed as preferred include: docetaxel, doxorubicin, and cyclophosphamide (TAC); doxorubicin, cyclophosphamide (AC); dose-dense AC with sequential paclitaxel; AC followed by weekly paclitaxel; and docetaxel plus cyclophosphamide (TC). Other regimens included in the guidelines are: fluorouracil, doxorubicin, and cyclophosphamide (FAC/CAF) or cyclophosphamide, epirubicin, and fluorouracil (FEC/CEF); epirubicin and cyclophosphamide (EC); cyclophosphamide, methotrexate and fluorouracil (CMF); AC with sequential docetaxel administered every 3 weeks; AC with sequential paclitaxel administered every 3 weeks; doxorubicin, paclitaxel, cyclophosphamide each as a single agent for four cycles given every 2 weeks (dose-dense A – T– C); and FEC followed by docetaxel. The adjuvant chemotherapy guideline also includes specific representative doses and schedules for the recommended adjuvant chemotherapy regimens (see BINV-J). Recent studies document substantial improvement in outcome with the incorporation of trastuzumab in the adjuvant treatment of HER2-positive breast cancer (see Adjuvant trastuzumab therapy).

New to the 2009 version of the guidelines is the preferred versus other designation for adjuvant chemotherapy regimens. The purpose of this distinction is to convey the sense of the Panel regarding the relative efficacy and toxicity of the regimens.[191] Factors considered by the Panel include the efficacy, toxicity, and treatment schedules of the regimens. This initial attempt at categorizing preferred regimens will be followed in the future by a more comprehensive, systematic evaluation of comparative effectiveness which will also include cost considerations. Summarized below are clinical trial results focusing on treatment efficacy.

Studies of CMF chemotherapy versus no chemotherapy have shown disease-free and overall survival advantages with CMF chemotherapy.[2,192] Studies using CAF/FAC (cyclophosphamide, doxorubicin, 5-fluorouracil) chemotherapy have shown that the use of full-dose chemotherapy regimens is important.[193] In the Early Breast Cancer Trialists' overview of polychemotherapy, comparison of anthracycline-containing regimens with CMF showed a 12% further reduction in the annual odds of recurrence (P = 0.006) and an 11% further reduction in the annual odds of death (P = 0.02) with anthracycline-containing regimens.[192] Based on these data, the Panel qualified the appropriate chemotherapy regimens by the statement that anthracycline-containing regimens are preferred for node-positive patients. The Early Breast Cancer Trialists' analysis, however, did not consider the potential interaction between HER2 tumor status and efficacy of anthracycline-containing versus CMF chemotherapy regimens. Retrospective analysis has suggested that the superiority of anthracycline-containing chemotherapy may be limited to the treatment of those breast cancers that are HER2-positive.[66,68,70,161,194,195] The retrospective finding across several clinical trials that anthracycline-based chemotherapy may be more efficacious in patients whose tumors are HER2-positive has led to a footnote stating that anthracycline-based chemotherapy may be superior to non-anthracycline-containing regimens in the adjuvant treatment of such patients (see BINV-J).

Doxorubicin and cyclophosphamide chemotherapy for 4 cycles has been studied in randomized trials, resulting in relapse-free and overall survival equivalent to CMF chemotherapy.[196-198] No benefit from dose escalation of either doxorubicin or cyclophosphamide was shown.[199,200]

The results of two randomized trials comparing AC chemotherapy with or without sequential paclitaxel chemotherapy in women with axillary node-positive breast cancer suggest improved disease-free rates, and results from one of the trials showed an improvement in overall survival with the addition of paclitaxel.[200,201] On retrospective analysis, the apparent advantage of the paclitaxel-containing regimen appears greater in women with ER-negative breast cancers.

A randomized trial evaluated the use of concurrent versus sequential chemotherapy (doxorubicin followed by paclitaxel followed by cyclophosphamide versus doxorubicin plus cyclophosphamide followed by paclitaxel) given either every two weeks with filgrastim support versus every three weeks. The results show no significant difference between the two chemotherapy regimens, but demonstrate a 26% reduction in hazard of recurrence (P=0.01) and a 31% reduction in the hazard of death (P=0.013) for the dose-dense regimens.[202]

Two randomized prospective trials of CEF chemotherapy in axillary lymph node-positive breast cancer are available. In one trial, premenopausal women with node-positive breast cancer were randomized to receive classic CMF therapy versus CEF chemotherapy using high-dose epirubicin. Both ten-year relapse-free survival (52% vs. 45%; P = 0.007) and overall survival (62% vs. 58%; P =0.085) favored the CEF arm of the trial.[203] The second trial compared CEF given all intravenously every 3 weeks at 2 dose levels of epirubicin (50 mg/m^2 vs. 100 mg/m^2) in premenopausal and postmenopausal women with node-positive breast cancer. Five-year disease-free survival (55% vs. 66%; P =0.03) and overall survival (65% vs. 76%; P =0.007) both favored the epirubicin 100 mg/m^2 arm.[204] Another trial compared 2 dose levels of EC chemotherapy with CMF chemotherapy in women with node-positive breast cancer.[205] 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. An additional randomized trial in women with axillary lymph node-positive breast cancer compared six cycles of FEC with three cycles of FEC followed by three cycles of docetaxel.[206] Five-year disease-free survival (78.4% versus 73.2%, adjusted P=0.012) and overall survival (90.7% versus 86.7%, P=0.017) were superior with sequential FEC followed by docetaxel.

Final results from a randomized trial comparing docetaxel, doxorubicin, and cyclophosphamide (TAC) versus FAC chemotherapy in axillary lymph node-positive breast cancer demonstrated that TAC is superior to FAC.[207] Estimated 5-year disease-free survival with TAC was 75% and FAC 68% (hazard ratio 0.72; 95% CI 0.59-0.88; P=0.001) and survival 87% with TAC and 81% with FAC (hazard ratio 0.70; 95% CI 0.53-0.91; P=0.008). Disease-free survival favored TAC in both ER-positive and ER-negative tumors.

The Eastern Cooperative Oncology Group E1199 study was a four arm trial that randomized 4,950 women to receive AC chemotherapy followed by either paclitaxel or docetaxel given by either an every three weekly schedule or a weekly schedule.[208,209] At a median 63.8 months follow-up, no statistically significant differences in disease-free or overall survival were observed when comparing paclitaxel to docetaxel or weekly versus every 3 weekly administration. In a secondary series of comparisons, weekly paclitaxel was superior to every 3-weekly paclitaxel in disease-free survival (hazard ratio 1.27, 95% CI 1.03 – 1.57; P=0.006) and overall survival (hazard ratio 1.32, 95% CI 1.02-1.72; P=0.01), and every 3-weekly docetaxel was superior to every 3-weekly paclitaxel in disease-free survival (hazard ratio 1.23, 95% CI 1.00-1.52; P-0.02) but not in overall survival.[208]

Combination docetaxel and cyclophosphamide (TC) was compared with AC chemotherapy in a trial that randomized 1016 women with stage I – III breast cancer.[210] At a median follow-up of 6.9 years, overall disease-free survival (85% versus 79%; P=0.018) and overall survival (88% versus 84%; P=0.045) were significantly improved with TC compared with AC.

Several retrospective studies have evaluated the potential interaction of chemotherapy benefit and ER status.[2,155] These studies assessed the effect of chemotherapy on the risk of breast cancer recurrence in patients with ER-positive tumors receiving adjuvant endocrine therapy

when compared with patients with ER-negative tumor status not undergoing adjuvant endocrine therapy. These analyses suggest that the benefits of chemotherapy are significantly greater in patients with ER-negative disease. For example, the results of Berry et al. demonstrated that 22.8% more patients with ER-negative tumors survived without disease for 5 years if they received chemotherapy; this benefit was only 7% for patients with ER-positive tumors receiving chemotherapy.[155] The guideline therefore includes a recommendation for endocrine therapy and consideration of chemotherapy for patients with node-negative disease and tumors characterized as ER-positive which are greater than 1 cm and HER2-negative or tumors 0.6 to 1.0 cm that are moderately/poorly differentiated or with unfavorable features (see BINV-6).

Adjuvant trastuzumab therapy

Trastuzumab is a humanized, monoclonal antibody with specificity for the extracellular domain of the human epidermal growth factor receptor 2 (HER2/neu; HER2).[211] Results of five randomized trials testing trastuzumab as adjuvant therapy have been reported.[73-76] In NSABP B-31 patients with HER2-positive, node-positive breast cancer were randomly assigned to 4 cycles of AC every three weeks followed by paclitaxel 4 cycles every three weeks or the same regimen with 52 weeks of trastuzumab commencing with the paclitaxel. In the North Central Cancer Treatment Group (NCCTG) N9831 trial, patients with HER2-positive breast cancer that was node-positive, or, if node-negative, with primary tumors greater than 1 cm in size if ER- and PR-negative or greater than 2 cm in size if ER- or PR-positive, were similarly randomized except that paclitaxel was given by a low dose weekly schedule for 12 weeks and a third arm delayed trastuzumab until the completion of paclitaxel. The B-31 and NCCTG N9831 trials were jointly analyzed with the merged control arms for both trials compared with the merged arms using trastuzumab begun concurrently with the paclitaxel.[73] There were 3968 patients included in the joint analysis performed at 4 years median follow-up. A 52% reduction in the risk of recurrence (hazard ratio 0.48; 95% CI 0.41-0.57; P<0.0001) and a 35% reduction in the risk of death (hazard ratio 0.65; 95% CI 0.51-0.84; log-rank P = 0.0007) were documented.[212] Similar significant effects on disease-free survival were observed when results of the NSABP B-31 and NCCTG N9831 trials were analyzed separately. Cardiac toxicity was increased in patients treated with trastuzumab.[73,213,214] In the adjuvant trastuzumab trials, the rates of grade III/IV congestive heart failure (CHF) or cardiac-related death for patients receiving treatment regimens containing trastuzumab ranged from 0% (FinHer trial) to 4.1% (NSABP B-31 trial) overall.[73-76,213,214] The frequency of cardiac dysfunction appears to be related to both age and baseline left ventricular ejection fraction. An analysis of data from N9831 showed the 3-year cumulative incidence of congestive heart failure or cardiac death to be 0.3%, 2.8% and 3.3% in the arms of the trial without trastuzumab, with trastuzumab following chemotherapy, and with trastuzumab initially combined with paclitaxel, respectively.[214] The acceptable rate of significant cardiac toxicity observed in the trastuzumab adjuvant trials in part reflects rigorous monitoring for cardiac dysfunction. Furthermore, concerns have been raised regarding the long-term cardiac risks associated with trastuzumab therapy based on results of follow-up evaluations of cardiac function in patients enrolled in some of these trials.[215,216]

A third trial (HERA) (N=5081) tested trastuzumab for one or for two years compared to none following all local therapy and a variety of standard chemotherapy regimens in patients with node-positive disease or node-negative disease with tumor ≥ 1 cm.[74] At a median follow-up of one year, comparing one year versus not of trastuzumab, trastuzumab resulted in a 46% reduction in the risk of recurrence compared to no trastuzumab (hazard ratio 0.54; 95% CI 0.43-0.67; P < 0.0001), no difference in overall survival, and acceptable cardiac toxicity. The two year data indicate that 1-year of trastuzumab therapy is associated with

an overall survival benefit when compared with observation (hazard ratio for risk of death=0.66; 95% CI, 0.47-0.91; P=0.0115).[217]

The Breast Cancer International Research Group (BCIRG) 006 study randomized 3,222 women with HER2-positive, node-positive or high-risk node negative breast cancer to AC followed by docetaxel, AC followed by docetaxel plus trastuzumab for one year, or carboplatin, docetaxel plus trastuzumab for one year.[75] At 36 months of follow-up, patients receiving AC followed by docetaxel with trastuzumab (AC→TH) had a hazard ratio for disease-free recurrence of 0.61 (95% CI, 0.48-0.76; P<0.0001) when compared with the group of patients in the control arm receiving the same chemotherapy regimen without trastuzumab (AC→T). The hazard ratio for disease-free survival was 0.67 (95% CI, 0.54-0.83; P=0.0003) when patients in the carboplatin/docetaxel/ trastuzumab (TCH) containing arm were compared to patients in the control arm. No statistically significant difference in the hazard ratio for disease-free survival was observed between the two trastuzumab-containing arms. An overall survival advantage was reported for patients in both trastuzumab-containing arms relative to the control arm (hazard ratio for AC-TH vs AC-T=0.59; 95% CI, 0.42-0.85; P=0.004; hazard ratio for TCH vs AC-T=0.66; 95% CI, 0.47-0.93; P=0.017). Cardiac toxicity was significantly lower in the TCH arm (8.6% patients with >10% relative decline in left ventricular ejection fraction) compared with the AC-TH arm (18%; P<0.0001); differences in cardiac toxicity between the TCH arm and the AC-T control arm (10%) were not significant.

A fifth trial (FinHer) randomized 1010 women to either 9 weeks of vinorelbine followed by 3 cycles of FEC chemotherapy versus docetaxel for 3 cycles followed by 3 cycles of FEC chemotherapy.[76] Patients (N=232) with HER2-positive cancers that were either node-positive or node-negative and ≥ 2 cm and progesterone receptor-negative were further randomized to receive or not trastuzumab for 9 weeks during the vinorelbine or docetaxel portions of the chemotherapy only. With a median follow-up of 3 years, the addition of trastuzumab was associated with a reduction in risk of recurrence (hazard ratio 0.42; 95% CI 0.21-0.83; P=0.01). No statistically significant differences in overall survival (hazard ratio 0.41; 95% CI 0.16 – 1.08; P=0.07) or cardiac toxicity were observed with the addition of trastuzumab.

All of the adjuvant trials of trastuzumab demonstrate clinically significant improvements in disease-free survival, and the combined analysis from the NSABP B31 and NCCTG N9831 trials, and the HERA trial, significant improvement in overall survival with the use of trastuzumab in patients with high-risk, HER2-positive breast cancer. Therefore, regimens from each of these trials are included as trastuzumab-containing adjuvant regimen choices in the guideline (category 1) (see BINV-J). The benefits of trastuzumab are independent of ER status.[73] On the basis of these studies, the Panel has designated use of trastuzumab with chemotherapy as a category 1 recommendation in patients with HER2-positive tumors >1cm. The Panel recommends AC followed by paclitaxel with trastuzumab for 1 year commencing with the first dose of paclitaxel as a preferred trastuzumab-containing adjuvant regimen since the efficacy of this regimen has been demonstrated in two randomized clinical trials, and it has been associated with significant improvements in overall survival. The TCH regimen is also classified as a preferred regimen, especially in those with risk factors for cardiac toxicity, given the results of BCIG 006 study that demonstrated superior disease-free survival in patients receiving either TCH or AC followed by docetaxel plus trastuzumab both compared with AC followed by docetaxel alone. Since patients with borderline FISH (Pathvysion®) scores of greater than 2.0 to 2.2 HER2 genes/chromosome 17/cell in early-stage breast cancer were eligible for the adjuvant trials, the Panel cannot recommend exclusion of these patients from adjuvant treatment with trastuzumab if HER2 tumor status remains equivocal following retesting by the same or a

complementary method (see BINV-A). The Panel has also included a recommendation for consideration of adjuvant trastuzumab in women with node-negative tumors that are 0.6-1.0 cm (see BINV-5; BINV-7). Some support for this recommendation comes from results of a retrospective study of 1245 women with early-stage breast cancer tumors characterized as T1pN0.[218] Ten-year breast cancer specific survival and 10-year recurrence-free survival were 85% and 75%, respectively, in women with tumors characterized as HER2-positive, ER-positive, and 70% and 61%, respectively, in women with HER2-positive, ER-negative tumors. In addition, subgroup analyses from several of the randomized trials have shown consistent benefit of trastuzumab irrespective of tumor size or nodal status.[212, 219] However, the recommendation for consideration of trastuzumab in patients with HER2-positive, ER-negative tumors that are 0.6-1.0 cm is designated as category 3 because patients with tumors < 1 cm were not included in the available randomized trials, their risk overall for recurrence is relatively low, and the risk of cardiac toxicity diminishes the overall benefit.

Adjuvant therapy of favorable histology tumors

The Guidelines provide systemic treatment recommendations for the favorable-histology invasive breast cancers, such as tubular and colloid cancers, based on tumor size and axillary lymph node status (see BINV-9). If used, the treatment options for endocrine therapy, chemotherapy, and sequencing of treatment with other modalities are similar to those of the usual histology breast cancers. The vast majority of tubular breast cancers are both ER-positive and HER2-negative. Thus, the pathology evaluation and accuracy of the ER and/or HER2 determination should be questioned if a tubular breast cancer is found to be ER-negative and/or HER2-positive. Should a breast cancer be histologically identified as a tubular or colloid (mucinous) breast cancer and be confirmed as ER-negative, then the tumor should be treated according to the guideline for the usual histology, ER-negative breast cancers. The Panel acknowledges that prospective data regarding systemic adjuvant therapy of favorable histology tumors is lacking.

Medullary carcinoma is an uncommon variant of infiltrating ductal carcinoma characterized by high nuclear grade, lymphocytic infiltration, a pushing tumor border, and the presence of a syncytial growth pattern. It was previously thought that medullary carcinoma has a lower potential for metastases and a better prognosis than typical infiltrating ductal carcinoma. However, the best available evidence suggests that the risk of metastases equals that of other high-grade carcinomas, even for cases that meet all the pathologic criteria for typical medullary carcinoma. Furthermore, typical medullary carcinoma is uncommon, and there is marked interobserver variation in diagnosing this entity. Many cases classified as medullary carcinoma do not have all the pathologic features on subsequent pathologic review. Given these facts, there is concern that patients may be harmed if a high-grade infiltrating ductal carcinoma is misclassified as typical medullary carcinoma and this classification used as the basis for withholding otherwise indicated adjuvant systemic therapy. Therefore, the NCCN Panel believes that including medullary carcinoma with other special histology cancers that carry a very favorable prognosis and often do not require systemic therapy is not appropriate. The Panel recommends that cases classified as medullary carcinoma be treated as other infiltrating ductal carcinomas based on tumor size, grade, and lymph node status.

Stage III Invasive Breast Cancer

The staging evaluation for patients with stage III invasive breast cancer is similar to the one for patients with stage I or stage II disease (see BINV-13). The workup includes history and physical exam, a complete blood cell count, platelet count, liver function and alkaline phosphatase tsts, chest imaging, pathology review, pre-chemotherapy determination of tumor ER/PR receptor status and HER2 status, diagnostic bilateral

mammogram and breast ultrasound as clinically warranted. The performance of other studies, such as a breast MRI, a bone scan (category 2B) and abdominal imaging with CT (with or without pelvic CT), ultrasound or MRI (all category 2B) are optional unless directed by symptoms or other abnormal study results. The Panel recommends that use of PET or PET/CT scans should generally be discouraged for the evaluation of stage III disease, except in those situations where other staging studies are equivocal or suspicious. Although there is some very limited evidence demonstrating the utility of PET scanning in the staging of patients with locally advanced disease,[48,51] the Panel considers biopsy of equivocal or suspicious sites to be more likely than PET scanning to provide useful staging information for these patients. Genetic counseling is recommended if the patient is considered to be at high risk of hereditary breast cancer as defined by the NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Guidelines

Operable locally advanced breast cancer (clinical stage T3N1M0)

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

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

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

The workup of locally advanced breast cancer is described on BINV-13. For patients with inoperable non-inflammatory locally advanced disease at presentation, the initial use of anthracycline-based preoperative chemotherapy with or without a taxane is standard therapy.[220] Patients with locally advance breast cancer that is HER2-positive should receive an initial chemotherapy program that incorporates preoperative trastuzumab (BINV-J). Local therapy following a clinical response to preoperative chemotherapy usually consists of (1) total mastectomy with level I/II axillary lymph node dissection, with or without delayed breast reconstruction, or (2) lumpectomy and level I/II axillary dissection. Both local treatment groups are considered to have sufficient risk of local recurrence to warrant the use of chest wall (or breast) and supraclavicular node irradiation. If internal mammary lymph nodes are involved, they should also be irradiated. In the absence of detected internal mammary node involvement, consideration may be given to including the internal mammary lymph nodes in the radiation field (category 3) (see BINV-14). Adjuvant therapy may involve completion of planned chemotherapy regimen course if not completely preoperatively, followed by endocrine therapy in patients with hormone receptor-positive disease (see BINV-14). Up to one year of total trastuzumab therapy should be completed, if the tumor is HER2-positive (category 1). Capecitabine can be administered as a radiation sensitizer for patients at high risk of local recurrence (category 2B), if not given preoperatively. Endocrine therapy and trastuzumab can be administered concurrent with radiation therapy if indicated. If capecitabine is administered as a radiation sensitizer, trastuzumab may be given concurrently.

Patients with an inoperable stage III tumor with disease progression during preoperative chemotherapy should be considered for palliative breast irradiation in an attempt to enhance local control. In all subsets of patients, further systemic adjuvant chemotherapy after local therapy is felt to be standard. Tamoxifen (or an aromatase inhibitor if postmenopausal) should be added for those with hormone receptor-positive tumors, and trastuzumab should be given to those with HER2-positive tumors. Post-treatment follow-up for women with stage III disease is the same as for women with earlier-stage, invasive breast cancer. Treatment recommendations for inflammatory locally advanced breast cancer are described on IBC-1.

Post-therapy Surveillance and Follow-up

Post-therapy follow-up is optimally performed by members of the treatment team and includes the performance of regular physical examinations and mammography. In patients undergoing breast-conserving therapy, the first follow-up mammogram should be performed 6 - 12 months after the completion of breast-conserving radiation therapy (category 2B). The routine performance of alkaline phosphatase and liver function tests are not included in the Guidelines.[221-223] In addition, the Panel notes no evidence to support the use of "tumor markers" for breast cancer, and routine bone scans, CT scans, MRI scans, PET scans, or ultrasound examinations in the asymptomatic patient provide no advantage in survival or ability to palliate recurrent disease and are, therefore, not recommended.[48,224]

The use of dedicated breast MRI may be considered as an option for post-therapy surveillance and follow-up in women at high risk of bilateral disease, such as carriers of *BRCA 1/2* mutations. Rates of contralateral breast cancer following either breast-conserving therapy or mastectomy have been reported to be increased in women with *BRCA 1/2* mutations when compared with patients with sporadic breast cancer.[225-227] (see NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Guidelines; NCCN Breast Cancer Screening and Diagnosis Guidelines).

The Panel recommends that women with intact uteri who are taking tamoxifen should have yearly gynecologic assessments and rapid evaluation of any vaginal spotting that might occur because of the risk of tamoxifen-associated endometrial carcinoma in postmenopausal women[228] (see BINV-15). The performance of routine endometrial biopsy or ultrasonography in the asymptomatic woman is not recommended. Neither test has demonstrated utility as a screening test in any population of women. The vast majority of women with tamoxifen-associated uterine carcinoma have early vaginal spotting.

Symptom management for women on adjuvant endocrine therapies often requires treatment of hot flashes and the treatment of concurrent depression. Venlafaxine has specifically been studied and is an effective intervention in decreasing hot flashes.[229] Recent evidence has suggested that concomitant use of tamoxifen with certain selective serotonin reuptake inhibitors (SSRIs) (eg, paroxetine and fluoxetine) may decrease plasma levels of endoxifen, an active metabolite of tamoxifen.[230,231] These SSRIs may interfere with the enzymatic conversion of tamoxifen to endoxifen by inhibiting a particular isoform of cytochrome P-450 enzyme (CYP2D6) involved in the metabolism of tamoxifen. However, the SSRIs citalopram and venlafaxine appear to have only minimal effects on tamoxifen metabolism.

Premenopausal women who experience early ovarian failure secondary to adjuvant chemotherapy and postmenopausal women who are treated with an aromatase inhibitor are at increased risk for the development of osteopenia or osteoporosis with an associated increased risk of bone fracture. The guideline thus recommends monitoring of bone health during surveillance in these high risk women,[232] and supplemental calcium and vitamin D (see BINV-15). The use of a bisphosphonate is generally the preferred intervention to

improve or maintain bone mineral density for women with breast cancer and osteopenia or osteoporosis. A dental examination with preventive dentistry prior to initiation of bisphosphonate therapy is recommended.

A special situation arises in women who are premenopausal at diagnosis, who develop amenorrhea during or following treatment, and for whom the use of an aromatase inhibitor is considered. The continuation or return of ovarian function following chemotherapy with or without amenorrhea has been documented.[189,190] If an aromatase inhibitor is considered in women with amenorrhea following treatment, baseline levels of estradiol and gonadotropin followed by serial monitoring of these hormones should be performed if endocrine therapy with an aromatase inhibitor is initiated[190] (see BINV-K). Bilateral oophorectomy assures postmenopausal status in young women with therapy-induced amenorrhea and may be considered prior to initiating therapy with an aromatase inhibitor in a young woman.

Follow-up also includes assessment of patient adherence to ongoing medication regimens such as endocrine therapies. Predictors of poor adherence to medication include the presence of side effects associated with the medication, and incomplete understanding by the patient of the benefits associated with regular administration of the medication.[233] The Panel recommends the implementation of simple strategies to enhance patient adherence to endocrine therapy, such as direct questioning of the patient during office visits, as well as brief, clear explanations on the value of taking the medication regularly and the therapeutic importance of longer durations of endocrine therapy (see BINV-15).

Stage IV Metastatic or Recurrent Breast Cancer

The staging evaluation of women who present with metastatic or recurrent breast cancer includes history and physical exam, the performance of a CBC, platelet count, liver function tests, chest imaging, bone scan, radiographs of any long or weight-bearing bones that are painful or appear abnormal on bone scan, consideration of CT or MRI scan of the abdomen and pelvis, biopsy documentation of first recurrence if possible, and determination of hormone receptor status (ER and PR) and HER2 status if not previously performed. The Panel generally discourages the use of PET or PET/CT scans for the evaluation of patients with recurrent disease, except in those situations where other staging studies are equivocal or suspicious. Although there is limited, mostly retrospective, evidence to support the use of PET scanning to guide treatment planning through determination of the extent of disease in select patients with recurrent or metastatic disease,[48,51,234,235] the Panel considers biopsy of equivocal or suspicious sites to be more likely than PET scanning to provide accurate staging information in this population of patients. Genetic counseling may be recommended if patient is considered to be at high risk of hereditary breast cancer as defined by the NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Guidelines.

Local disease only

Patients with local recurrence only are divided into 3 groups: those who had been treated initially by mastectomy alone, mastectomy with radiation therapy and those who had received breast-conserving therapy (see BINV-16). Mastectomy-treated patients should undergo surgical resection of the local recurrence (if it can be accomplished without heroic surgery) and involved-field radiation therapy to chest and internal mammary nodes (if the chest wall was not previously treated or if additional radiation therapy may be safely administered). 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 radiation therapy if no prior radiation has been given. Women with a local recurrence of disease after initial breast-conserving therapy should undergo a total mastectomy and axillary lymph node dissection

if not previously performed. After local treatment, women with local recurrences only should be considered for limited duration systemic chemotherapy or endocrine therapy similar to that outlined in the adjuvant chemotherapy section.

The Guidelines include consideration of the addition of hyperthermia to irradiation for localized recurrences/metastasis (category 3) (see BINV-16). There have been several prospective randomized trials comparing radiation to radiation plus hyperthermia in the treatment of locally advanced/recurrent cancers, primarily breast cancer chest wall recurrences.[236,237] While there is heterogeneity among the study results, a recent series with strict quality assurance demonstrated a statistically significant increase in local tumor response and greater duration of local control with the addition of hyperthermia to radiation compared to radiation alone.[237] No differences in overall survival have been demonstrated. Delivery of local hyperthermia is technically demanding and requires specialized expertise and equipment (eg, the monitoring of temperatures and management of possible tissue burns). The Panel thus recommends that the use of hyperthermia be limited to treatment centers with appropriate training, expertise, and equipment. The addition of hyperthermia generated substantial discussion and controversy among the Panel and is a category 3 recommendation.

Systemic disease

The systemic treatment of breast cancer recurrence or stage IV disease prolongs survival and enhances quality of life but is not curative. Therefore, treatments associated with minimal toxicity are preferred. Thus, the use of the minimally toxic endocrine therapies is preferred to the use of cytotoxic therapy whenever reasonable.[238]

Guideline stratification for therapy in systemic disease

Patients with recurrence of breast cancer or metastatic breast cancer at diagnosis are initially stratified according to whether or not bone metastasis is present (see section on Bisphosphonates, below). These 2 patient subsets are then stratified further by tumor hormone receptor and HER2 status (see BINV-16).

Bisphosphonates

Bisphosphonate treatment is of value in patients with metastatic breast cancer in bone.[232,239] Women with bone metastasis, especially if lytic, should be given a bisphosphonate (eg, pamidronate or zoledronic acid) in combination with calcium citrate and vitamin D if expected survival is 3 months or longer and creatinine levels are below 3.0 mg/dL (category 1).[232,240-245] Bisphosphonates are given in addition to chemotherapy or endocrine therapy. Zoledronic acid may be superior to pamidronate in lytic breast metastasis.[246,247]

There are extensive data from randomized trials in support of the use of bisphosphonates for patients with metastatic disease to bone. The randomized clinical trial data includes the use of zoledronic acid and pamidronate in the United States and ibandronate and clodronate in European countries.[241,242,247-252] In metastatic bone disease, bisphosphonate treatment is associated with fewer skeletal-related events, pathologic fractures, and less need for radiation therapy and surgery to treat bone pain.

The use of bisphosphonates in metastatic disease is a palliative care measure. No impact on overall survival has been observed in patients treated with bisphosphonates. The data indicate that zoledronic acid and pamidronate may be given on a 3-5 weekly schedule in conjunction with antineoplastic therapy (ie, endocrine therapy, chemotherapy or biologic therapy). The use of bisphosphonates should be accompanied by calcium and vitamin D supplementation with daily doses of calcium of 1200 to 1500mg and Vitamin D_3 400 – 800 IU. Recommended agents for use in the United States are pamidronate 90mg intravenously over 2 hours or zoledronic acid 4mg intravenously over 15 minutes. The original studies continued treatment for up to 24

months; however, there are limited long-term safety data indicating treatment can continue beyond that time.[252-254] The risk of renal toxicity necessitates monitoring of serum creatinine prior to administration of each dose and dose reduction or discontinuation if renal function is reduced. Current clinical trial results support the use of bisphosphonates for up to two years. Longer durations of bisphosphonate therapy may provide additional benefit, but this has not yet been tested in clinical trials.

Osteonecrosis of the jaw, a recently reported complication of bisphosphonate treatment, has been described. In a review of more than 16,000 cancer patients, an increased risk of jaw or facial bone surgery along with an increased risk of being diagnosed with inflammatory conditions or osteomyelitis of the jaw with the use of intravenous bisphosphonates was documented. An absolute risk of 5.48 events per 100 patients treated was seen, with an increase in risk associated with an increase in cumulative dose of drug.[255]

A dental examination with preventive dentistry intervention is recommended prior to treatment with intravenous bisphosphonates and dental procedures during treatment with intravenous bisphosphonates should be avoided if at all possible. Additional risk factors for the development of osteonecrosis of the jaw include administration of chemotherapy or corticosteroids and poor oral hygiene with periodontal disease and dental abscess.[256]

Confirmation of metastatic disease by imaging including x-ray, CT or MRI; and initial evaluation of serum calcium, creatinine, phosphorous and magnesium levels should be undertaken prior to the initiation of intravenous bisphosphonate treatment in patients with metastatic disease. Frequent measurement of calcium, phosphorous and magnesium may be prudent since hypophosphatemia and hypocalcemia have been reported.

Endocrine therapy

Women with recurrent or metastatic disease characterized by tumors that are ER- and/or PR-positive are appropriate candidates for initial endocrine therapy (see BINV-17). In postmenopausal women with previous antiestrogen therapy and who are within one year of antiestrogen exposure, evidence supports the use of a selective aromatase inhibitor as the preferred first-line therapy for their recurrent disease.[257,258] For postmenopausal women who are antiestrogen naive or who are more than 1 year from previous antiestrogen therapy, the aromatase inhibitors appear to have superior outcome compared with tamoxifen, although the differences are modest.[259-262] 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 endocrine therapy as for postmenopausal women. In premenopausal women without previous exposure to an antiestrogen, initial treatment is with an antiestrogen alone, or ovarian suppression or ablation plus endocrine therapy as for postmenopausal women (preferred)[263] (see BINV-17).

Many premenopausal and postmenopausal women with hormone-responsive breast cancer benefit from sequential use of endocrine therapies at the time of disease progression. Therefore, women with breast cancers who respond to an endocrine maneuver with either shrinkage of the tumor or long-term disease stabilization (clinical benefit) should receive additional endocrine therapy at the time of disease progression (see BINV-20). Additional endocrine therapies for second-line and subsequent therapy are listed in the endocrine algorithm (see BINV-L). The antiestrogen fulvestrant is an option for the

treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer previously treated with an antiestrogen or an aromatase inhibitor. Fulvestrant lacks the estrogen agonistic activity of tamoxifen and is well tolerated as a single monthly gluteal intramuscular injection. Fulvestrant appears to be at least as effective as anastrozole in patients whose disease progressed on previous tamoxifen,[264,265] and a reanalysis of these studies suggests a longer duration of response favoring fulvestrant.[266] A phase II study of fulvestrant in postmenopausal women with advanced breast cancer and disease progression following aromatase inhibitor therapy documented a partial response rate of 14.3% with an additional 20.8% of patients achieving stable disease for at least 6 months.[267] Furthermore, the clinical benefit rates of exemestane and fulvestrant observed in a phase III trial of postmenopausal women with hormone receptor-positive advanced breast cancer who experienced disease progression on prior nonsteroidal aromatase inhibitor therapy were comparable (32.2% vs. 31.5%; P=0.853).[268] Endocrine therapies in postmenopausal women include selective, nonsteroidal aromatase inhibitors (anastrozole and letrozole); steroidal aromatase inhibitors (exemestane); pure anti-estrogens (fulvestrant); progestin (megestrol acetate); androgens (fluoxymesterone); and high-dose estrogen (ethinyl estradiol). In premenopausal women, therapies include LHRH agonists (goserelin and luprolide); surgical or radiotherapeutic oophorectomy; progestin (megestrol acetate); androgens (fluoxymesterone); and high-dose estrogen (ethinyl estradiol). After second-line endocrine therapy, little high-level evidence exists to assist in selecting the optimal sequence of endocrine therapy.

Endocrine therapy may be active in patients with negative ER and PR determinations, especially on the primary tumor and in soft tissue disease and/or bone dominant disease.[269-271] Endocrine therapy is also associated with relatively low toxicity. Further, false negative determinations of ER and PR tumor status are not unusual and the hormone receptor status of primary and metastatic sites of disease may differ. The Panel recommends consideration of a trial of endocrine therapy for patients with disease characterized as hormone receptor-negative or hormone receptor-positive and endocrine refractory, and localized to the bone or soft tissue only or asymptomatic visceral disease, irrespective of HER2 tumor status (see BINV-18; BINV-19).

Cytotoxic chemotherapy

Women with hormone receptor-negative tumors not localized to the bone or soft tissue only or that are associated with symptomatic visceral metastasis, or that have hormone receptor-positive tumors that are refractory to endocrine therapy, should receive chemotherapy (see BINV-18; BINV-19). A variety of chemotherapy regimens are felt to be appropriate, as outlined in the treatment algorithm (see BINV-M). Combination chemotherapy generally provides higher rates of objective response and longer time to progression, in comparison to single agent chemotherapy. Combination chemotherapy is, however, associated with an increase in toxicity, and is of little survival benefit.[272-275] Furthermore, administering single agents sequentially decreases the likelihood that dose reductions will be needed. Thus, the Panel finds little compelling evidence that combination chemotherapy is superior to sequential single agents. Standard clinical practice is to continue first-line chemotherapy until progression. Adverse effects may require dose reduction and cessation of chemotherapy prior to disease progression. Limited information suggests that progression-free survival can be prolonged with the use of continuous chemotherapy versus shorter course chemotherapy.[276,277] Due to the lack of overall survival differences, the use of prolonged versus shorter chemotherapy needs to be weighted against the detrimental effects of continuous chemotherapy on overall quality of life.

Listed on BINV-M are single cytotoxic agents and combination chemotherapy regimens recommended by the Panel for the treatment

of patients with metastatic disease. Single agents are categorized as either preferred or other single agents on the basis of a balance of the efficacy, toxicity, and treatment schedules of the drugs. Likewise, combination regimens are categorized as either preferred or other combinations.

Preferred chemotherapies thus include sequential single agents or combination chemotherapy. Among preferred first-line single agents, the Panel includes: the anthracyclines- doxorubicin, epirubicin, and pegylated liposomal doxorubicin; the taxanes,- paclitaxel, docetaxel, and albumin-bound paclitaxel; anti-metabolites- capecitabine and gemcitabine; and non-taxane microtubule inhibitors - 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); docetaxel, capecitabine; and gemcitabine, paclitaxel. Under the heading of other single agents are cyclophosphamide, cisplatin, etoposide orally (category 2B), vinblastine, mitoxantrone, ixabepilone, and fluorouracil by continuous infusion. As with endocrine therapy, sequential responses are often observed with chemotherapy, supporting the use of sequential single agents and combination chemotherapy regimens. The current guideline includes doses and schedules of these single agents and combination regimens for metastatic breast cancer (see BINV-M).

A recent trial randomized 715 women with recurrent or metastatic breast cancer to first-line chemotherapy with paclitaxel with or without bevacizumab, a humanized monoclonal antibody against the vascular endothelial growth factor (VEGF).[278] This trial documented superior progression-free survival (11.8 months vs. 5.9 months; hazard ratio 0.60; P <0.001) favoring bevacizumab plus paclitaxel compared with paclitaxel alone. No significant difference in overall survival was observed when the 2 groups were compared.

Ixabepilone, an epothilone B analogue, is a new agent for treatment of recurrent or metastatic breast cancer as a single agent (category 2A) or in combination with capecitabine (category 2B), both in the “other active options” grouping (see BINV-M). Use of ixabepilone as monotherapy has been evaluated in several phase II trials of women with metastatic breast cancer: in a first-line setting in patients previously treated with anthracycline chemotherapy[279]; in patients with taxane-resistant metastatic breast cancer[280]; and in patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine.[281] In the phase II trials, objective response rate, median duration of response, and median overall survival duration was 41.5% (95% CI, 29.4% to 54.4%), 8.2 months (95% CI, 5.7 to 10.2 months), and 22.0 months (95% CI, 15.6 to 27.0 months) in the first line setting,[279] 12% (95% CI, 4.7% to 26.5%), 10.4 months, and 7.9 months for the taxane-resistant patients,[280] and 11.5% (95% CI, 6.3% to 18.9%), 5.7 months, and 8.6 months for the patients previously treated with an anthracycline, a taxane, and capecitabine.[281] In the study of Perez et al., grade 3/4 treatment-related toxicities included peripheral sensory neuropathy (14%) and neutropenia (54%).[281] In addition, a phase III study compared ixabepilone plus capecitabine to capecitabine alone in women with metastatic breast cancer which progressed after anthracycline and taxane treatment.[282] The primary endpoint, progression-free survival (PFS), was 5.8 months vs. 4.2 months (hazard ratio=0.75, 95% CI, 0.64 to 0.88; P=0.0003), and objective response rate was 35% vs. 14% (P<0.0001) in the 2 arms of the trial. No data on overall survival were reported, although the incidence of treatment-related death resulting from neutropenia was substantially higher in the combination arm.

Failure to achieve a tumor response to 3 sequential chemotherapy regimens or an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or greater is an indication for supportive therapy only. In this context, failure to respond to a chemotherapy regimen means the absence of even a marginal response to the use of a given chemotherapy regimen. Response to a chemotherapy regimen followed by progression of disease is not considered a failure to experience response.

Patients with metastatic breast cancer frequently develop a number of anatomically localized problems that may benefit from local irradiation, surgery, or regional chemotherapy (eg, intrathecal methotrexate for leptomeningeal carcinomatosis).

HER2-targeted therapy

Patients with tumors that are HER2-positive may derive benefit from treatment with trastuzumab as a single agent or in combination with selected chemotherapeutic agents, or the combination of capecitabine plus lapatinib for those refractory to therapy with an anthracycline, a taxane, and trastuzumab (BINV-19). The Panel recommends selecting patients for HER2-targeted therapy if their tumors are either positive for HER2 by FISH or 3+ by IHC. HER2 testing recommendations are described in the guideline (see BINV-A). Patients with tumors IHC 0 or 1+ for HER2 or FISH not amplified have very low rates of HER2-targeted response, and therapy with trastuzumab or lapatinib is not warranted.[283] Adequate standardization and validation of HER2 assays by FISH and IHC used in clinical practice is a concern, and data suggest that false-positive determinations are common.[59,61,64,65,284] Recommendations regarding HER2 testing have been published.[64,65]

In patients with metastatic breast cancer with HER2-positive tumors, first-line trastuzumab in combination with selected chemotherapeutics[78] or as a single agent[77,79] is recommended (see BINV-M). Randomized trials demonstrate benefit from adding trastuzumab to other agents including paclitaxel with or without carboplatin,[78,283,285,286] docetaxel,[286] and vinorelbine,[286] or as a single agent[79] for patients with HER2-positive disease. In addition, the combination of trastuzumab and capecitabine has also shown efficacy as a first-line trastuzumab-containing regimen in this population of patients.[287,288] The Panel believes the 27% frequency of significant cardiac dysfunction in patients treated with the combination of trastuzumab and doxorubicin/cyclophosphamide chemotherapy in the metastatic setting is too high for use of this combination outside the confines of a prospective clinical trial.[78,289]

The Panel recommends continuation of HER2 blockade for patients with HER2-positive metastatic breast cancer which progresses on first-line trastuzumab-containing regimens. This recommendation also applies to the relatively new class of patients who are diagnosed with HER2-positive metastatic disease following prior exposure to trastuzumab in the adjuvant setting. Several recent trials have demonstrated benefit of continuation of trastuzumab therapy following disease progression on a trastuzumab-containing regimen.[290-292] The regimen of capecitabine plus lapatinib is also an option for patients with HER2-positive disease following progression on a trastuzumab-containing regimen. A phase III study compared lapatinib plus capecitabine with capecitabine alone in women with advanced or metastatic breast cancer refractory to trastuzumab in the metastatic setting and with prior treatment with an anthracycline and a taxane in either the metastatic or adjuvant setting.[293] Time to progression was increased in the group receiving combination therapy when compared with the group receiving capecitabine monotherapy (8.4 months vs. 4.4 months; hazard ratio=0.49, 95% CI, 0.34-0.71; P<0.001). In addition, results from a phase III trial in which patients with heavily pretreated metastatic breast cancer and disease progression on trastuzumab therapy were randomly assigned to monotherapy with lapatinib or trastuzumab plus lapatinib showed that progression-free survival was

increased from 8.1 weeks to 12 weeks (P=0.008) with the combination.[294] The current guideline includes doses and schedules of representative chemotherapy single agents and regimens for use in combination with either trastuzumab or lapatinib for metastatic breast cancer, and for the combination of lapatinib and trastuzumab (see BINV-M). Based on the absence of data, the Panel does not recommend the addition of chemotherapy to the trastuzumab/lapatinib combination. The optimal duration of HER2-targeted therapy in patients with long-term disease control is unknown.

Surgery

The primary treatment approach recommended by the NCCN Panel for women with metastatic breast cancer and an intact primary tumor is systemic therapy, with consideration of surgery after initial systemic treatment for those women requiring palliation of symptoms or with impending complications, such as skin ulceration, bleeding, fungation, and pain.[295] Generally such surgery should be undertaken only if complete local clearance of tumor may be obtained and if other sites of disease are not immediately threatening to life. Alternatively, radiation therapy may be considered as an option to surgery. Often such surgery requires collaboration between the breast surgeon and the reconstructive surgeon to provide optimal cancer control and wound closure.

Recent retrospective studies suggest a potential survival benefit from complete excision of the in breast tumor in select patients with metastatic breast cancer.[296-299] Substantial selection biases exist in all of these studies and are likely to confound the study results.[300,301] Nevertheless, the Panel recognizes the need for randomized clinical trials that will address the risks and benefits of local therapy for patients with stage IV disease while eliminating selection biases. Patient enrollment in such trials is encouraged.

Special Situations

Paget's disease

Paget's disease of the breast is a rare manifestation of breast cancer characterized by neoplastic cells in the epidermis of the nipple areolar complex.[302] It most commonly presents with eczema of the areola, bleeding, ulceration, and itching of the nipple. The diagnosis is often delayed because of the rare nature of the condition and confusion with other dermatologic conditions. There is an associated cancer elsewhere in the breast in up to about 80-90% of cases.[303-305] The associated cancers are not necessarily located adjacent to the nipple areolar complex and may be either DCIS or invasive cancer.

Women with clinical signs that raise suspicion for Paget's disease require a complete history and physical examination and diagnostic breast imaging (see PAGET-1). Any breast lesion identified by imaging or examination should be evaluated according to the NCCN Breast Screening and Diagnostic Guidelines. The skin of the nipple areolar complex should undergo surgical biopsy including the full thickness of the epidermis including at least a portion of any clinically involved nipple areola complex. When biopsy of the nipple areola complex is positive for Paget's disease, breast MRI is recommended to define the extent of disease and identify additional disease (see PAGET-2; BINV-B).[305,306]

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

Management of Paget's disease has traditionally been total mastectomy with axillary dissection. Total mastectomy remains a reasonable option for patients regardless of the absence or presence of

an associated breast cancer.[303] Recent data demonstrate that satisfactory local control may be achieved with breast-conserving surgery including the excision with negative margins of any underlying breast cancer along with resection of the nipple areolar complex followed by whole breast radiation therapy.[307-312] The risk of ipsilateral breast recurrence after breast-conserving nipple areola complex resection and radiation therapy with or without an associated cancer is similar to that with breast-conserving surgery and radiation therapy with the typical invasive or in situ cancer.

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

Axillary lymph node staging is not necessary when breast-conserving therapy is used to treat Paget's disease with underlying DCIS in the absence of evidence of invasive cancer following clinical examination, imaging evaluation, and full thickness skin biopsy of the involved nipple areola complex. In the presence of an underlying invasive breast cancer treated with breast-conserving surgery, axillary surgery should be performed according to the Surgical Axillary Staging guideline (see BINV-C). In cases treated by total mastectomy, axillary staging is recommended for patients with invasive disease and should also be considered for patients with underlying DCIS without evidence of invasive disease because the final pathology may reveal an invasive cancer in the mastectomy specimen and the mastectomy precludes subsequent sentinel node biopsy. Two recently reported retrospective studies have provided evidence for a high degree of accuracy in the identification of the sentinel node(s) in patients with Paget's disease.[313,314] Patients treated with breast conservation should receive whole breast radiation. Extended field radiation to regional lymph nodes should be used in cases of an associated invasive breast cancer with involved lymph nodes as for any breast cancer as described in BINV-2. A radiation boost should be considered to the site of the resected nipple areolar complex and any associated resected cancer site, if applicable.

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

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

Phyllodes tumors of the breast are rare tumors comprised of both stromal and epithelial elements.[315] Phyllodes tumors exist in benign, borderline, and malignant subtypes, although there is not uniform agreement on the criteria for assigning subtype or for predicting biological behavior.[316] Subtype of phyllodes tumor appears less important for risk of recurrence than does the margin of tumor-free resection achieved by surgical treatment. Diagnosis of phyllodes tumors prior to excisional biopsy/lumpectomy is uncommon. Phyllodes tumors occur in an older age distribution than fibroadenoma, a younger age distribution than the invasive ductal and lobular cancers, and with a mean age in the 40's.[317] Phyllodes tumors often enlarge rapidly and are

usually painless. Phyllodes tumors often appear on ultrasound and mammography as fibroadenomas, and fine needle aspiration cytology and even core needle biopsy are inadequate to reliably distinguish phyllodes tumors from fibroadenoma.[317] Thus in the setting of a large or rapidly enlarging clinical fibroadenoma, excisional biopsy should be considered to pathologically exclude a phyllodes tumor. Patients with the Li-Fraumeni Syndrome (germ line p53 mutation, see NCCN Genetic/Familial High Risk Assessment Guidelines) have an increased risk of phyllodes tumors.[318] Local recurrences of phyllodes tumors are the most common site of recurrence. Most distant recurrences occur in the lung, and may be solid nodules or thin-walled cavities.

Treatment of phyllodes tumors (which includes benign, borderline and malignant subtypes) is with local surgical excision with tumor free margins of 1 cm or greater. Lumpectomy or partial mastectomy is the preferred surgical therapy. Total mastectomy is necessary only if negative margins cannot be obtained by lumpectomy or partial mastectomy[319] (see PHYLL-1). Since phyllodes tumors rarely metastasize to the axillary lymph nodes, surgical axillary staging or axillary lymph node dissection is not necessary unless the lymph nodes are pathologic on clinical examination.[320] In those patients who experience a local recurrence, resection of the recurrence with wide tumor-free surgical margins should be performed (see PHYLL-2). Some members of the Panel recommend local radiation therapy of the remaining breast or chest wall following resection of a local recurrence, but this recommendation is controversial (category 2B).[321]

While the epithelial component of most phyllodes tumors contains estrogen receptor (58%) and/or progesterone receptor (75%),[322] endocrine therapy has no proven role in the treatment of phyllodes tumors. Similarly, there is no evidence that adjuvant cytotoxic chemotherapy provides benefit in reduction of recurrences or death. In the rare patient who experiences a systemic recurrence (usually in the lung), treatment should be as recommended in the NCCN Soft Tissue Sarcoma Guidelines.

Breast cancer during pregnancy

Breast cancer occurring concurrent with pregnancy is an infrequent clinical event. In a California registry study, there were 1.3 breast cancers diagnosed per 10,000 live births.[323] Unfortunately, breast cancer during pregnancy is most often axillary lymph node-positive and with larger primary tumor size. Histologically the tumors are poorly differentiated, more frequently estrogen and progesterone receptor-negative and approximately 30% are HER2-positive.[324,325] The diagnosis is often delayed because neither the patient nor the physician suspects malignancy.

Evaluation of the pregnant patient with suspected breast cancer should include a physical examination with particular attention to the breast and regional lymph nodes. Mammogram of the breast with shielding can be done safely and the accuracy is reported to be greater than 80%.[326] Ultrasound of the breast and regional lymph nodes can be used to assess the extent of disease and also to guide biopsy. Ultrasound has been reported to be abnormal in up to 100% of breast cancers occurring during pregnancy.[326] Biopsies for cytologic evaluation of a suspicious breast mass may be done with a fine needle aspiration (FNA) of the breast and suspicious lymph nodes. However, the preferred technique is core needle biopsy. This provides tissue for histologic confirmation of invasive disease as well as providing adequate tissue for hormone receptor and HER2 analyses.

Staging assessment of the pregnant patient with breast cancer may be guided by clinical disease stage. For clinically node-negative T1-T2 tumors, a chest x-ray (with shielding), liver function and renal function assessment and complete blood count with differential are appropriate. In patients who have clinically node-positive or T3 breast lesions, in addition to the aforementioned, an ultrasound of the liver and

consideration of a screening MRI of the thoracic and lumbar spine without contrast may be employed. The documentation of the presence of metastases may alter the treatment plan and influence the patient's decision regarding maintenance of the pregnancy. Assessment of the pregnancy should include a maternal fetal medicine consultation and review of antecedent maternal risks such as hypertension, diabetes and complications with prior pregnancies. Documentation of fetal growth and development and fetal age by means of ultrasonographic assessment is appropriate. Estimation of the date of the delivery will help with systemic chemotherapy planning. In addition, maternal fetal medicine consultation should include counseling regarding maintaining or terminating pregnancy. Counseling of the pregnant patient with breast cancer should include a review of the treatment options which include mastectomy or breast-conserving surgery as well as the use of systemic therapy. The most common surgical procedure has been modified radical mastectomy. However, Kuerer et al. have shown that breast-conserving surgery is possible if radiation therapy can be delayed to the postpartum period,[327] and breast-conserving therapy during pregnancy does not appear to have a negative impact on survival.[327,328] When surgery is performed at 25 weeks gestation or later, obstetrical and prenatal specialists must be on site and immediately available in the event of precipitous delivery of a viable fetus.

Although there are a limited number of isolated case reports and small retrospective studies evaluating use of sentinel lymph node biopsy in the pregnant patients,[329,330] the sensitivity and specificity of the procedure has not been established in this setting. Thus, there are insufficient data on which to base recommendations for its use in the pregnant woman. Decisions related to use of sentinel lymph node biopsy in pregnancy should be individualized. A recent review of the relative and absolute contraindications to sentinel node biopsy concluded that sentinel node biopsy should not be offered to pregnant women under 30 weeks gestation.[331] There are limited data with only case reports and estimations of fetal radiation dose regarding use of radioactive tracer (eg, technectium 99m sulfur colloid).[332-334] Isosulfan blue or methylene blue dye for sentinel node biopsy procedures is not recommended during pregnancy.

The indications for systemic chemotherapy are the same in the pregnant patient as in the non-pregnant breast cancer patient, although chemotherapy should not be administered at any point during the first trimester of pregnancy. The greatest experience in pregnancy has been with anthracycline and alkylating agent chemotherapy.[335,336] Collected data of chemotherapy exposure in utero indicates that the first trimester has the greatest risk of fetal malformation.[337,338] Fetal malformation risks in the second and third trimester are approximately 1.3%, not different than that of fetuses not exposed to chemotherapy during pregnancy. If systemic therapy is initiated, fetal monitoring prior to each chemotherapy cycle is appropriate. Chemotherapy during pregnancy should not be given after week 35 of pregnancy or within 3 weeks of planned delivery in order to avoid the potential for hematologic complications at the time of delivery. Recent data from a single institution prospective study indicate that FAC chemotherapy (5-FU 500 mg/m^2 IV day 1 and 4, doxorubicin 50 mg/m^2 by IV infusion over 72 hours and cyclophosphamide 500 mg/m^2 IV day 1) may be given with relative safety during the second and third trimesters of pregnancy.[336] Ondansetron, lorazepam and dexamethasone can be used as part of the pre-chemotherapy antiemetic regimen. As reported by Gwyn et al., the median gestational age at delivery was 38 weeks, more than 50% of the patients had vaginal delivery and there have been no fetal deaths. An update of this experience reported on 57 women treated with FAC in the adjuvant or neoadjuvant setting. There were 57 live births. A survey of parents/guardians reported on the health of 40 children. There was 1 child with Down's syndrome and 2 with congenital abnormalities (club foot; congenital bilateral ureteral reflux).

The children are reported to be healthy and progressing well in school.[336,339]

Ondansetron, lorazepam and dexamethasone can be used as part of the pre-chemotherapy antiemetic regimen.

There are limited data on the use of taxanes during pregnancy and their use is not recommended during pregnancy.[340-344] If a taxane is indicated clinically, it may be used in the post-delivery setting. Preferred chemotherapy choices are those doxorubicin-based regimens that have already been evaluated in pregnant patients.

There are only case reports of trastuzumab use during pregnancy. [345-352] Five of these case reports indicated oligo- or anhydramnios with administration of trastuzumab; fetal renal failure occurred in one case. If trastuzumab is otherwise indicated, it should be administered in the postpartum period.

A single case report of first trimester exposure to lapatinib during treatment for breast cancer reported an uncomplicated delivery of a healthy female neonate.[353]

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

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

Inflammatory breast cancer

Inflammatory breast cancer (IBC) is a rare, aggressive form of breast cancer estimated to account for 1%-6% of breast cancer cases in the United States.[354,355] IBC is a clinical diagnosis that requires erythema and dermal edema (peau d'orange) of a third or more of the skin of the breast with a palpable border to the erythema. IBC is classified according to the 6th edition of the *AJCC Cancer Staging Manual* as stage IIIB, stage IIIC, or stage IV breast cancer, depending on the degree of nodal involvement and whether distant metastases are present. The primary tumor of IBC is classified as T4d by definition, even when no mass is specifically apparent in the breast. On radiographic imaging, findings of skin thickening and, in some cases, an underlying mass is observed. Despite use of the term "inflammatory", the characteristic clinical features of IBC are due to blockage of dermal lymphatics by tumor emboli. Although a biopsy is required to evaluate for the presence of cancer in breast tissue and the dermal lymphatics, a diagnosis of IBC is based of clinical findings, and dermal lymphatic involvement is neither required for, nor sufficient by itself, to assign a diagnosis of IBC.[5,356] The differential diagnosis includes cellulitis of the breast and mastitis.

In the past, IBC has often been placed under the general heading of locally advanced breast cancer. There is a growing body of evidence that IBC patients, when compared with those with noninflammatory forms of locally advanced breast cancer, are more likely to have disease that is HER2-positive and hormone receptor-negative[357,358], to have a less favorable prognosis[359,360] (ie, disease-free survival at 5 years were 35% and 50% for inflammatory vs. non-inflammatory status [P=0.020][361]), and to be younger at the time of disease presentation.[362] The Panel acknowledges that studies focusing on genetic characterization of IBC are needed to more clearly define IBC as a disease entity and to optimize treatment.[363,364] Nevertheless, current evidence provides justification for a separate guideline for the work-up and treatment of patients diagnosed with IBC (see IBC-1).

Women with a clinical/pathologic diagnosis of IBC without distant metastasis (stage T4d, N0-N3, M0) should undergo a thorough staging evaluation. Recommendations include a complete history and physical

examination involving a complete blood cell count and platelet count. Evaluations for the presence of distant metastasis include liver function testing, bone scan (category 2B), CT imaging of the chest, abdomen and pelvis (category 2B; category 2A for CT imaging of the chest when pulmonary symptoms are present). Evaluation of the extent of local disease is determined using diagnostic bilateral mammogram, with the addition of ultrasound as necessary. A breast MRI scan is optional. A pathology review and pre-chemotherapy determinations of tumor hormone-receptor and HER2-receptor status should be performed.

The treatment of patients with IBC should involve a combined modality approach.[355] The benefit of preoperative chemotherapy followed by mastectomy over preoperative chemotherapy alone in patients with IBC was shown in a retrospective analysis in which lower local recurrence rates and longer disease-specific survival were reported for the combined modality approach.[365] Results from a retrospective study of patients with IBC performed over a 20-year period at M.D. Anderson demonstrated that initial treatment with doxorubicin-based chemotherapy followed by local therapy (ie, radiation therapy or mastectomy, or both) and additional postoperative chemotherapy resulted in a 15-year disease-free survival rate of 28%.[366] Additional support for the use of anthracycline-based preoperative chemotherapy comes from the only randomized trial of patients with IBC. In this study, 5-year survival rates of 44% were observed when epirubicin/cyclophosphamide-based regimens were administered as initial therapy.[367] A recent retrospective study has demonstrated that addition of a taxane to an anthracycline-based regimen improved PFS and overall survival in patients with ER-negative IBC.[368] A recent systematic review found evidence for an association between the intensity of preoperative therapy and the likelihood of a pathologic complete response.[369]

It has been known for many years that primary surgical treatment of patients with IBC is associated with very poor outcomes.[370] Use of breast-conserving surgery in patients with IBC has been associated with poor cosmesis, and limited data suggest that rates of local recurrence may be higher when compared with mastectomy.

The Panel recommends preoperative chemotherapy with an anthracycline-based regimen with or without taxanes for the initial treatment of patients with IBC (see IBC-1). Inclusion of trastuzumab in the chemotherapy regimen is recommended for patients with HER2-positive disease. Patients with a clinical/pathologic diagnosis of IBC should not be treated with pre-chemotherapy surgery. Patients responding to preoperative chemotherapy should undergo mastectomy with axillary lymph node dissection; breast-conserving therapy is not recommended for patients with IBC. Any remaining planned chemotherapy should be completed postmastectomy followed sequentially by endocrine therapy in patients with hormone receptor-positive disease. If the IBC is HER2 positive, completion of one year of trastuzumab is recommended. Finally, post-mastectomy chest wall and regional node irradiation is recommended following the completion of any planned chemotherapy (see IBC-1). Mastectomy is not recommended for patients with IBC who do not respond to preoperative chemotherapy. Additional systemic chemotherapy and/or preoperative radiation should be considered for these patients, and patients responding to this secondary therapy should undergo mastectomy and subsequent treatment as described above. Patients with stage IV or recurrent IBC should be treated according to the guideline for recurrence/stage IV disease (BINV-15 to BINV-20).

Axillary breast cancer

Axillary metastasis from an occult breast cancer represents approximately 3-5% of breast cancers. Evidence to support recommendations on the management of these patients comes from a

limited number of retrospective studies involving small numbers of patients[371,372,373] (see also references therein). Although treatment of women with axillary metastases from an unknown primary tumor has typically involved mastectomy and axillary nodal dissection, some of these patients have also been successfully treated with axillary nodal dissection followed by radiation therapy.[372,373]

There is some evidence to indicate that MRI of the breast can facilitate the identification of occult breast cancer, and help select those patients most likely to benefit from mastectomy. For example, in a study of 40 patients with biopsy-proven breast cancer in the axilla, and a negative or indeterminate mammogram, MRI identified the primary breast lesion in 70% of the patients.[373] In addition, of the 7 patients with a negative MRI who subsequently underwent axillary lymph node dissection and radiation therapy to the whole breast, no evidence of local recurrence was evident at a median follow-up of 19 months.

The NCCN Occult Primary Guidelines provide guidance on the diagnosis and initial work-up of patients with a suspicious axillary mass in the absence of any signs of a primary tumor. (It is also worth noting that a small subset of these patients may have a primary cancer in the axillary tail of the breast.) These guidelines also provide recommendations for additional work-up, including chest and abdominal CT to evaluate for evidence of distant metastases for patients diagnosed with adenocarcinoma (or carcinoma not otherwise specified) of the axillary nodes without evidence of a primary breast lesion; in particular, breast MRI and ultrasound are recommended. Axillary ultrasound should also be performed.

Patients with MRI-positive disease should undergo further evaluation with ultrasound or MRI-guided biopsy and receive treatment according to the clinical stage of the breast cancer. Treatment recommendations for those with MRI-negative disease are based on nodal status. For patients with T0,N1,M0 disease, options include either mastectomy plus axillary nodal dissection or axillary nodal dissection plus whole breast irradiation with or without nodal irradiation (see BINV-H). Systemic chemotherapy, endocrine therapy, or trastuzumab is given according to the recommendations for Stage II or III disease (BINV-4). Neoadjuvant chemotherapy, trastuzumab, and endocrine therapy should be considered for patients with T0, N2-N3,M0 disease followed by axillary nodal dissection and mastectomy as for patients with locally advanced disease (BINV-14).

Summary

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

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

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