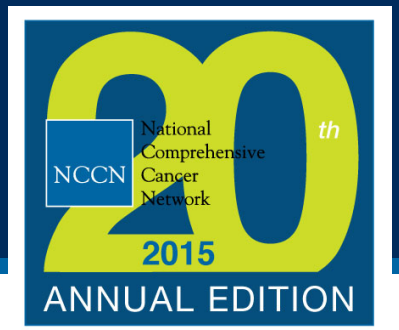


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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer

Version 3.2015

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

See NCCN Categories of Evidence and Consensus.

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Breast Cancer Updates

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Updates in Version 3.2015 of the NCCN Guidelines for Breast Cancer from Version 2.2015 include:

DISCUSSION

- The Discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 2.2015 of the NCCN Guidelines for Breast Cancer from Version 1.2015 include:

BINV-F

- The following sentence has been removed from the second paragraph: "This can be achieved with brachytherapy or electron beam or photon fields. "

BINV-G

- Changed "Focally positive" to "Diffusely positive pathologic margins."

BINV-M

- Changed page heading from "Subsequent Endocrine Therapy for Systemic Disease" to "Endocrine Therapy for Recurrent or Stage IV Disease."
- Added palbociclib + letrozole as a therapuetic option for postmenopausal patients with ER-positive, HER2-negative metastatic breast cancer.
- Added the following footnote: "Palbociclib in combination with letrozole may be considered as a treatment option for first-line therapy for postmenopausal patients with ER-positive, HER2-negative metastatic breast cancer."

Updates in Version 1.2015 of the NCCN Guidelines for Breast Cancer from Version 3.2014 include:

DCIS-1

- Modified footnote "h" stating Complete axillary lymph node dissection should not be performed in the absence of evidence of invasive cancer or proven axillary metastatic disease 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 should be strongly 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.

BINV-2

- Modified the statement "Radiation therapy should follow chemotherapy when chemotherapy is indicated" to "It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated."

BINV-3

- Changed "close margins" to "negative margins but <1 mm."
- Negative axillary nodes and tumor ≤5 cm and margins ≥1 mm, "No radiation therapy" added a footnote stating: "Postmastectomy radiation therapy may be considered for patients with multiple high-risk recurrence factors."

BINV-5

- Changed pN0 "Consider adjuvant endocrine therapy" to "Consider adjuvant endocrine therapy ± adjuvant chemotherapy with trastuzumab (category 2B)."
- Added footnote "aa" stating "A pertuzumab-containing regimen can be administered to patients with greater than or equal to T2 or greater than or equal to N1, HER2-positive, early-stage breast cancer." (Also applies to BINV-7)

BINV-6

- Added footnote "bb" stating "The 21-gene RT-PCR assay recurrence score can be considered in select patients with 1–3 involved ipsilateral axillary lymph nodes to guide the additon of combination chemotherapy to standard hormone therapy. A retrospective analysis of a prospective randomized trial suggests that the test is predictive in this group similar to its performance in node-negative disease."

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Discussion

Updates in Version 1.2015 of the NCCN Guidelines for Breast Cancer from Version 3.2014 include:

BINV-7

Changed pN0 "Consider no adjuvant therapy" to "Consider adjuvant chemotherapy with trastuzumab (category 2B).

BINV-10

Preoperative systemic therapy guideline, fulfills criteria for breast-conserving surgery except for tumor size. Added a footnote stating; "In cases where breast-conserving surgery may not be possible but patient will need chemotherapy, neoadjuvant treatment remains an acceptable option."

BINV-11

- Changed "Desires breast preservation" to "Preoperative systemic therapy" and "Does not desire breast preservation" to "Surgical resection."
- Clinically negative axillary lymph nodes, changed axillary "ultrasound" to "imaging."
- Moved "clipped with image-detectable marker; positive clipped lymph nodes must be moved if FNA or core biopsy was positive" from the algorithm to a new footnote. "Marking of sampled axillary nodes with a tattoo or clip should be considered to permit verification that the biopsy-positive lymph node has been removed at the time of definitive surgery."
- Added two new branch points:
  - "If lymph node FNA or core biopsy negative, SLNB can be performed before or after neoadjuvant systemic therapy"
  - "If lymph node FNA or core biopsy positive, axilla may be restaged after neoadjuvant systemic therapy; ALND should be performed if axilla is clinically positive; SLNB or ALND can be performed if axilla is clinically negative"
- Added footnote "ff" stating "Among patients shown to be node-positive prior to neoadjuvant systemic therapy, SLNB has a >10% false-negative rate when performed after neoadjuvant systemic therapy. This rate can be improved by marking biopsied nodes to document their removal, using dual tracer, and by removing more than 2 sentinel nodes."

BINV-12

- Clarified footnote "ii" by deleting the term "early stage." The footnote now states: "A pertuzumab-containing regimen may be administered preoperatively to patients with greater than or equal to T2 or greater than or equal to N1, HER2-positive breast cancer." (Also applies to BINV-15)

BINV-15

- The following statement was added to this page "endocrine therapy alone may be considered for receptor-positive disease in postmenopausal patients."
- Added footnote "gg" stating "A number of chemotherapy regimens have activity in the preoperative setting. In general, those chemotherapy regimens recommended in the adjuvant setting may be considered in the preoperative setting. See Neoadjuvant/Adjuvant Chemotherapy (BINV-K). If treated with endocrine therapy, an aromatase inhibitor is preferred for postmenopausal women."
- Added a footnote stating "Administration of all chemotherapy prior to surgery is preferred."

BINV-16

- The following changes have been made to the Surveillance/Follow-up recommendations:
  - History and physical exam was changed from "every 4–6 mo for 5 y, then every 12 mo" to "1–4 times per year as clinically appropriate for 5 y, then annually."
  - Added "Educate, monitor, and refer for lymphedema management."
  - Added "In the absence of clinical signs and symptoms suggestive of recurrent disease, there is no indication for laboratory or imaging studies for metastases screening."

BINV-17

- Workup, changed "Determination of tumor ER/PR and HER2 status if unknown, originally negative or not overexpressed" to "Determination of tumor ER/PR and HER2 status on metastatic site." Added footnote"rr": "In clinical situations where a biopsy cannot be safely obtained but the clinical evidence is strongly supportive of recurrence, treatment may commence based on the ER/PR/HER2 status of the primary tumor."

BINV-18

- Systemic therapy, added "or de novo stage IV" with a new footnote "ww": "The role and timing of surgical removal of the primary in patients presenting with de novo stage IV disease is the subject of ongoing investigations."
- Footnote "ss" changed "The optimal schedule and duration of denosumab, zoledronic acid, or pamidronate are unknown" to "The optimal schedule for zoledronic acid is monthly x 12, then quarterly."

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Updates in Version 1.2015 of the NCCN Guidelines for Breast Cancer from Version 3.2014 include:

BINV-19
- Added footnote "yy" to the following nodes:
  - ER-and/or PR positive; HER2 positive
  - Prior endocrine therapy within 1 y – Postmenopausal

BINV-B
- Clinical Indications and Applications, removed the following bullet: "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)."

BINV-C
- Deleted "No therapy has been shown to preserve fertility in patients receiving chemotherapy."
- Added "Randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with ER-negative tumors may preserve ovarian function and diminish the lkelihood of chemotherapy-induced amenorrhea."
- Added "Smaller historical experiences in patients with ER-positive disease have reported conflicting results with regards to the protective effect of GNRH agonist therapy on fertility."

BINV-D
- Sentinel node positive: removed "Axillary dissection level I/II" as an option.
- Added footnote "4" stating: "For patients with clinically negative axillae who are undergoing mastectomy and for whom radiation therapy is planned, axillary radiation may replace axillary dissection level I/II for regional control of disease."

BINV-F
- First paragraph, added the following statement "The NCCN Panel accepts the definition of a negative margin as "No ink on the tumor," from the 2014 Society of Surgical Oncology-American Society for Radiation Oncology Consensus Guidelines on Margins."
- Added Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol. 2014 May 10;32(14):1507-15

BINV-F (continued)
- Second paragraph, added the following statement "A boost to the tumor bed is recommended in patients at higher risk (age <50 or high-grade disease, or patients with focally positive margins). This can be achieved with brachytherapy or electron beam or photon fields. Typical doses are 10–16 Gy at 2 Gy/fx."

BINV-H (2 of 2)
- First bullet, added the following statement "Nipple margin assessment is mandatory, and the nipple margin should be clearly designated."

BINV-I
- Whole Breast Radiation, modified the statement: "The breast should receive a dose of 45–50 Gy in ~~1.8-2 Gy per~~ 23–25 fractions, or 40–42.5 Gy in 15–16 fractions (short course is preferred)."
- Regional Nodal Radiation, replaced "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" with "Based on the modern post mastectomy radiation randomized trials and other recent studies, consider including the internal mammary lymph nodes when delivering regional nodal irradiation."

BINV-J
- Added a new footnote for premenopausal at diagnosis stating, "Aromatase inhibitor for 5 y + ovarian suppression may be considered as an alternative option based on SOFT and TEXT clinical trial outcomes." Pagani O, Regan M, Walley B, et al. Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer. N Engl J Med 2014; 371:107-118. July 10, 2014DOI: 10.1056/NEJMoa1404037.

BINV-K
- Other regimens for HER2-negative disease, added "AC (doxorubicin/ cyclophosphamide) every 3 weeks (category 2B)."
- Other regimens for HER2-positive disease, added "Docetaxel + cyclophosphamide + trastuzumab."
- Updated reference list.

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Updates in Version 1.2015 of the NCCN Guidelines for Breast Cancer from Version 3.2014 include:

BINV-N (1 of 7)
- Added the following to footnote"4": "Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab in the metastatic setting, may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy."

BINV-N (2 of 7)
- Modified dose schedule for docetaxel; "35 mg/m^2 IV weekly for 6 wks followed by a 2-week rest, then repeat."

BINV-N (3 of 7)
- Modified dose schedule for FAC chemotherapy; for "cycled every 21 days" removed "for 6 cycles."

BINV-N (6 of 7)
- Added reference "Rivera E, Mejia JA, Arun BJ, et al. Phase 3 study comparing the use of docetaxel on an every-3-week versus weekly schedule in the treatment of metastatic breast cancer. Cancer 2008 Apr 1;112(7):1455-61."

BINV-N (7 of 7)
- Added reference to support docetaxel/capecitabine chemotherapy combination; Mavroudis D, Papakotoulas P, Ardavanis A, et al. Randomized phase III trial comparing docetaxel plus epirubicin versus docetaxel plus capecitabine as first-line treatment in women with advanced breast cancer. Ann Oncol 21:48(2010).

PHYLL-1
- Added footnote "d" to wide excision without axillary staging: "There are 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 mastectomy), radiation therapy may be considered following the same principles that are applied to the treatment of soft tissue sarcoma."

PAGET-2
- Added the following treatment options:
  - Central lumpectomy including NAC with whole breast radiation therapy
    or
  - Total mastectomy[c] ± sentinel node biopsy with or without breast reconstruction
    or
  - Central lumpectomy including NAC ± sentinel node biopsy without radiation therapy (category 2B)
- Removed the following footnotes:
  - "With Paget's disease and no associated peripheral cancer, or with associated ER-positive DCIS, consider tamoxifen 20 mg per day for 5 years."
  - "With associated invasive breast cancer, treat with appropriate systemic adjuvant therapy."

PREG-1
- Modified footnote "c": replaced "trastuzumab" with "anti-HER2 therapy."

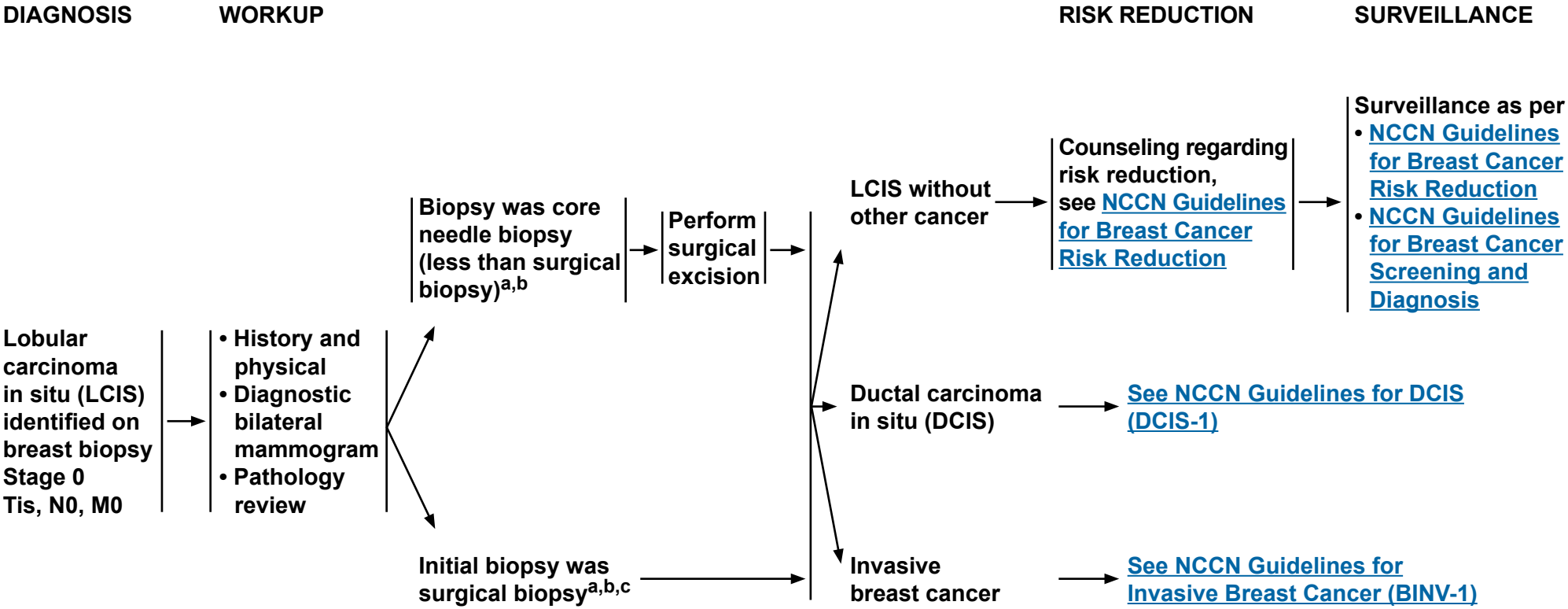
IBC-1
- Footnote "a": removed the following statement "...and with a palpable border to erythema."
- Footnote "j" is new to the page "A pertuzumab-containing regimen may be administered preoperatively to patients with HER2-positive IBC."

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Lobular Carcinoma in Situ

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[a]LCIS is present on initial biopsy (needle or surgical) or on final excision with or without other proliferative changes (atypical ductal or lobular hyperplasia).
[b]Some variants of LCIS (pleomorphic LCIS) may have a similar biological behavior to that of DCIS. Clinicians may consider complete excision with negative margins for pleomorphic LCIS, but outcomes data regarding the efficacy of surgical excision to negative margins are lacking. There are no data to support using radiotherapy in this setting.
[c]Multifocal/extensive LCIS involving >4 terminal ductal lobular units on a core biopsy may be associated with increased risk for invasive cancer on surgical excision.

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Ductal Carcinoma in Situ

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DIAGNOSIS	WORKUP	PRIMARY TREATMENT
DCIS Stage 0 Tis, N0, M0[a]	**• History and physical exam • Diagnostic bilateral mammogram • Pathology review[b] • Determination of tumor estrogen receptor (ER) status • Genetic counseling if patient is high risk for hereditary breast cancer[c] • Breast MRI[d,e] (optional)**	**Lumpectomy[f,g] without lymph node surgery[h] + whole breast radiation therapy[i,j,k,l,m] (category 1) or Total mastectomy with or without sentinel node biopsy[h,k] ± reconstruction[n] or Lumpectomy[f,g] without lymph node surgery[h] without radiation therapy[i,k,l,m] (category 2B)** → **See Postsurgical Treatment (DCIS-2)**

[a] See NCCN Guidelines for Breast Cancer Screening and Diagnosis.
[b] The panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. http://www.cap.org.
[c] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.
[d] See Principles of Dedicated Breast MRI Testing (BINV-B).
[e] The use of MRI has not been shown to increase likelihood of negative margins or decrease conversion to mastectomy. Data to support improved long-term outcomes are lacking.
[f] 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.
[g] See Margin Status in DCIS (DCIS-A).
[h] Complete axillary lymph node dissection should not be performed in the absence of evidence of invasive cancer or proven axillary metastatic disease 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 should be strongly 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.
[i] See Principles of Radiation Therapy (BINV-I).
[j] Complete resection should be documented by analysis of margins and specimen radiography. Post-excision mammography could also be performed whenever uncertainty about adequacy of excision remains.
[k] Patients found to have invasive disease at total mastectomy or re-excision should be managed as having stage I or stage II disease, including lymph node staging.
[l] See Special Considerations to Breast-Conserving Therapy Requiring Radiation Therapy (BINV-G).
[m] Whole-breast radiation therapy following lumpectomy reduces recurrence rates in DCIS by about 50%. Approximately half of the recurrences are invasive and half are DCIS. A number of factors determine that local recurrence risk: palpable mass, larger size, higher grade, close or involved margins, and age <50 years. If the patient and physician view the individual risk as “low,” some patients may be treated by excision alone. All data evaluating the three local treatments show no differences in patient survival.
[n] See Principles of Breast Reconstruction Following Surgery (BINV-H).

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DCIS POSTSURGICAL TREATMENT

Risk reduction therapy for ipsilateral breast following breast-conserving surgery:
Consider tamoxifen[o] for 5 years for:
- **Patients treated with breast-conserving therapy (lumpectomy) and radiation therapy[p] (category 1), especially for those with ER-positive DCIS.**
- **The benefit of tamoxifen for ER-negative DCIS is uncertain**
- **Patients treated with excision alone[p]**

Risk reduction therapy for contralateral breast:
- **Counseling regarding risk reduction[o]**
  See NCCN Guidelines for Breast Cancer Risk Reduction

→

SURVEILLANCE/FOLLOW-UP

- **Interval history and physical exam every 6–12 mo for 5 y, then annually**
- **Mammogram every 12 mo (and 6–12 mo postradiation therapy if breast conserved [category 2B])**
- **If treated with tamoxifen, monitor per NCCN Guidelines for Breast Cancer Risk Reduction**

[o]Some SSRIs like fluoxetine and paroxetine decrease the formation of endoxifen and 4-OH tamoxifen, active metabolites of tamoxifen, and may impact efficacy. Caution is advised about coadministration of these drugs with tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. At this time, based on current data the panel recommends against CYP2D6 testing for women being considered for tamoxifen therapy. Coadministration of strong inhibitors of CYP2D6 should be used with caution.

[p]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 Guidelines for Breast Cancer Risk Reduction).

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MARGIN STATUS IN DCIS

Substantial controversy exists regarding the definition of a negative pathologic margin in DCIS. Controversy arises out of the heterogeneity of the disease, difficulties in distinguishing the spectrum of hyperplastic conditions, anatomic considerations of the location of the margin, and inadequate prospective data on prognostic factors in DCIS.

Margins greater than 10 mm are widely accepted as negative (but may be excessive and may lead to a less optimal cosmetic outcome).

Margins less than 1 mm are considered inadequate.

With pathologic margins between 1–10 mm, wider margins are generally associated with lower local recurrence rates. However, close surgical margins (<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

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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
Stage IIIA
T3, N1, M0

→

WORKUP

- **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]**
- **Genetic counseling if patient is high risk for hereditary breast cancer[c]**
- **Breast MRI[d] (optional), with special consideration for mammographically occult tumors**
- **Fertility counseling if premenopausal[e]**
- **Assess for distress (See NCCN Guidelines for Distress Management)**

For clinical stage I-IIB, consider additional studies only if directed by signs or symptoms:[f]

- **Bone scan indicated if localized bone pain or elevated alkaline phosphatase**
- **Abdominal ± pelvic diagnostic CT or MRI indicated if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, or abnormal physical examination of the abdomen or pelvis**
- **Chest diagnostic CT (if pulmonary symptoms present)**

- **If clinical stage IIIA (T3, N1, M0) consider:**
- **Chest diagnostic CT**
- **Abdominal ± pelvic diagnostic CT or MRI**
- **Bone scan or sodium fluoride PET/CT[g] (category 2B)**
- **FDG PET/CT[h,i] (optional, category 2B)**

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

[a]The panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. http://www.cap.org.
[b]See Principles of HER2 Testing (BINV-A).
[c]See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.
[d]See Principles of Dedicated Breast MRI Testing (BINV-B).
[e]See Fertility and Birth Control (BINV-C).
[f]Routine systemic staging is not indicated for early breast cancer in the absence of symptoms.
[g]If FDG PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component, bone scan or sodium fluoride PET/CT may not be needed.
[h]FDG PET/CT can be performed at the same time as diagnostic CT. The use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.
[i]FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.

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

Lumpectomy with surgical axillary staging (category 1)[j,k,l]

- **≥4 positive[o] axillary nodes** → **Radiation therapy to whole breast with or without boost[p] to tumor bed (category 1), infraclavicular region, and supraclavicular area. Strongly consider radiation therapy to internal mammary nodes[q] (category 2B). It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated.**
- **1–3 positive axillary nodes** → **Radiation therapy to whole breast with or without boost[p] (to tumor bed (category 1). Strongly consider radiation therapy to infraclavicular supraclavicular area, internal mammary nodes[q] (category 2B). It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated.**

or

- **Negative axillary nodes** → **Radiation therapy to whole breast with or without boost[p] to tumor bed or consideration of partial breast irradiation (PBI) in selected patients.[p,r] It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated.[s]**

→ See BINV-4

Total mastectomy with surgical axillary staging[j,k,m] (category 1) ± reconstruction[n] → See Locoregional Treatment (BINV-3)

or

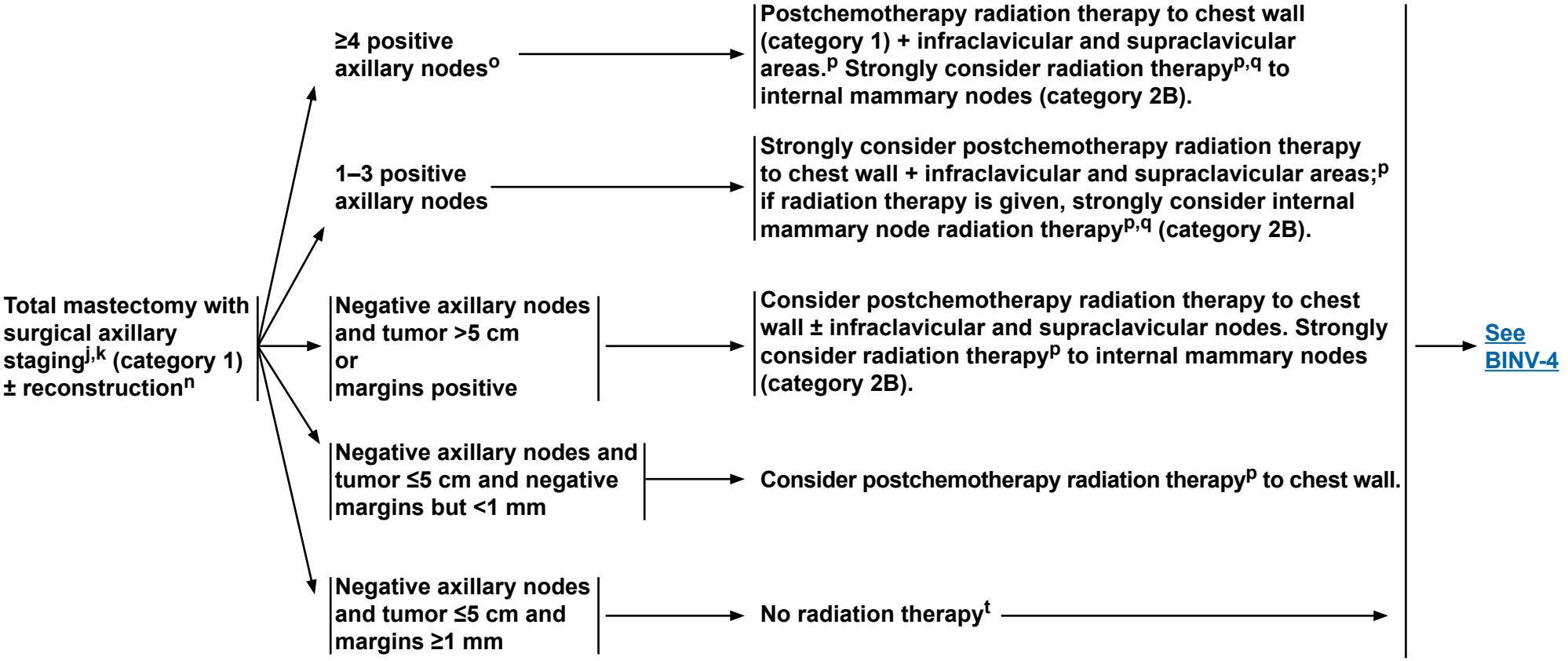
If T2 or T3 and fulfills criteria for breast-conserving therapy except for size[l] → Consider Preoperative Systemic Therapy Guideline (BINV-10)

[j] See Surgical Axillary Staging (BINV-D).
[k] See Axillary Lymph Node Staging (BINV-E) and Margin Status in Infiltrating Carcinoma (BINV-F).
[l] See Special Considerations to Breast-Conserving Therapy Requiring Radiation Therapy (BINV-G).
[m] Except as outlined in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian and the NCCN Guidelines for Breast Cancer Risk Reduction, prophylactic mastectomy of a breast contralateral to a known unilateral breast cancer is discouraged. When considered, the small benefits from contralateral prophylactic mastectomy for women with unilateral breast cancer must be balanced with the risk of recurrent disease from the known ipsilateral breast cancer, psychological and social issues of bilateral mastectomy, and the risks of contralateral mastectomy. The use of a prophylactic mastectomy contralateral to a breast treated with breast-conserving therapy is very strongly discouraged.
[n] See Principles of Breast Reconstruction Following Surgery (BINV-H).
[o] Consider imaging for systemic staging, including diagnostic CT or MRI, bone scan, and optional FDG PET/CT (category 2B) (See BINV-1).
[p] See Principles of Radiation Therapy (BINV-I).
[q] 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.
[r] PBI may be administered prior to chemotherapy.
[s] 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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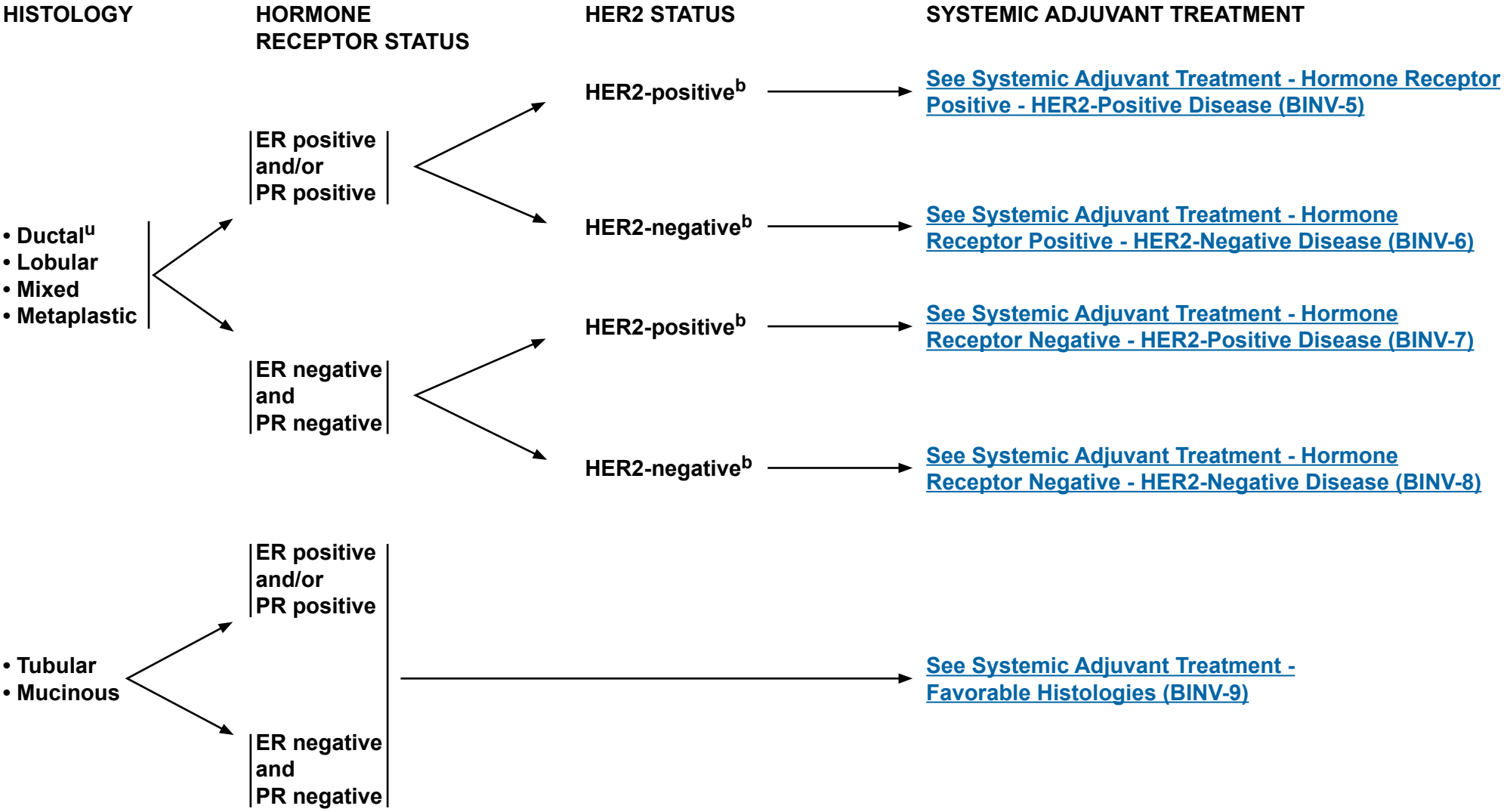
LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3, N1, M0



[j] See Surgical Axillary Staging (BINV-D).
[k] See Axillary Lymph Node Staging (BINV-E) and Margin Status in Infiltrating Carcinoma (BINV-F).
[n] See Principles of Breast Reconstruction Following Surgery (BINV-H).
[o] Consider imaging for systemic staging, including diagnostic CT or MRI, bone scan, and optional FDG PET/CT (category 2B) (See BINV-1).
[p] See Principles of Radiation Therapy (BINV-I).
[q] 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.
[t] Postmastectomy radiation therapy may be considered for patients with multiple high-risk recurrence factors.

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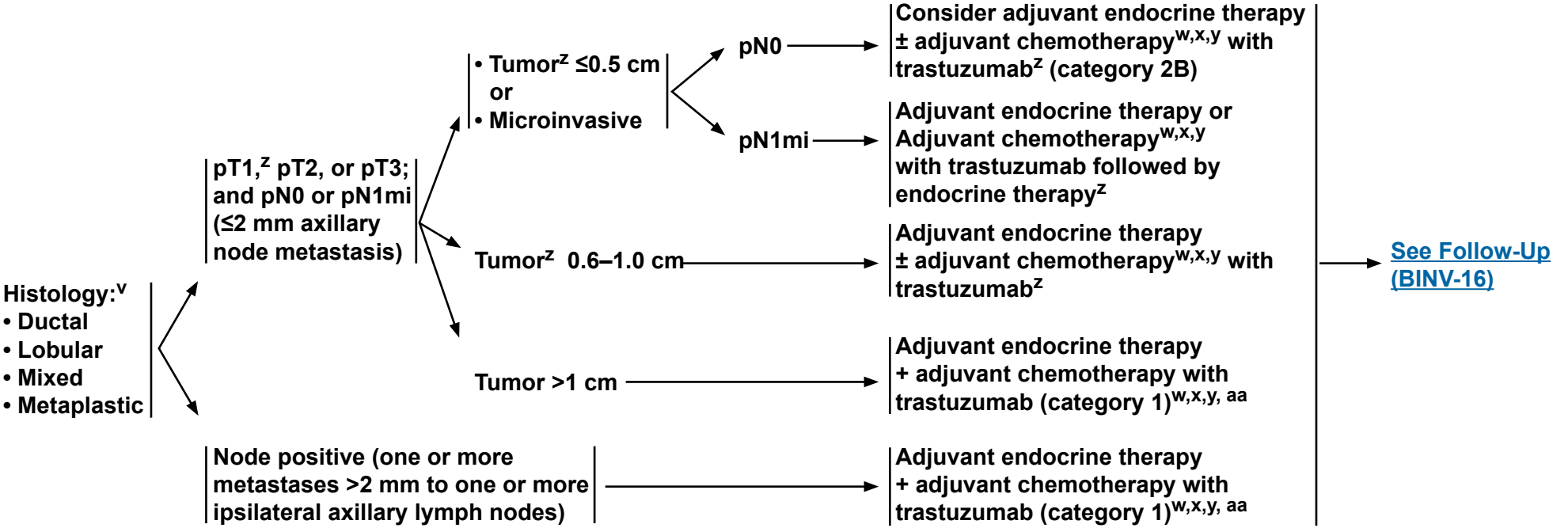


[b]See Principles of HER2 Testing (BINV-A).
[u]This includes medullary and micropapillary subtypes.

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



See Adjuvant Endocrine Therapy (BINV-J) and Neoadjuvant/Adjuvant Chemotherapy (BINV-K)

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

[v] 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.

[w] 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.

[x] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable.

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

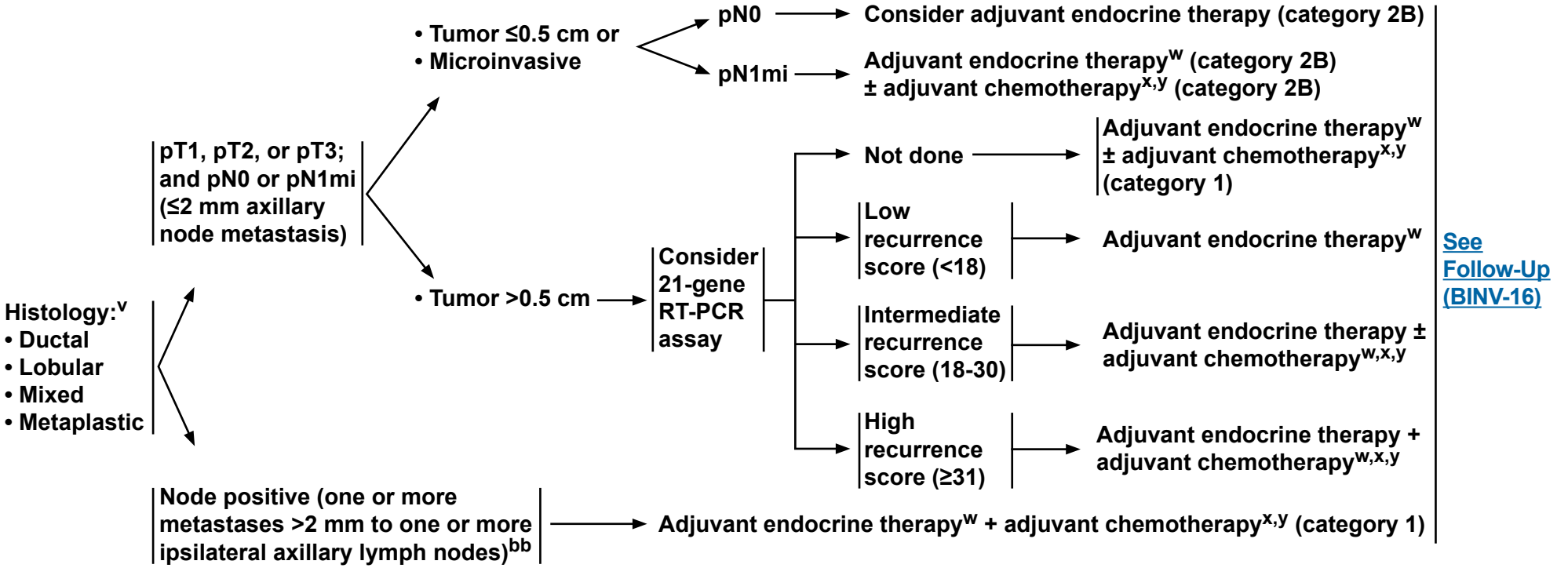
[z] The prognosis of patients with T1a and T1b tumors that are node negative is uncertain even when HER2 is amplified or over-expressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of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

[aa] A pertuzumab-containing regimen can be administered to patients with greater than or equal to T2 or greater than or equal to N1, HER2-positive, early-stage breast cancer.

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



See Adjuvant Endocrine Therapy (BINV-J) and Neoadjuvant/Adjuvant Chemotherapy (BINV-K)

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

[v] 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.

[w] 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.

[x] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable.

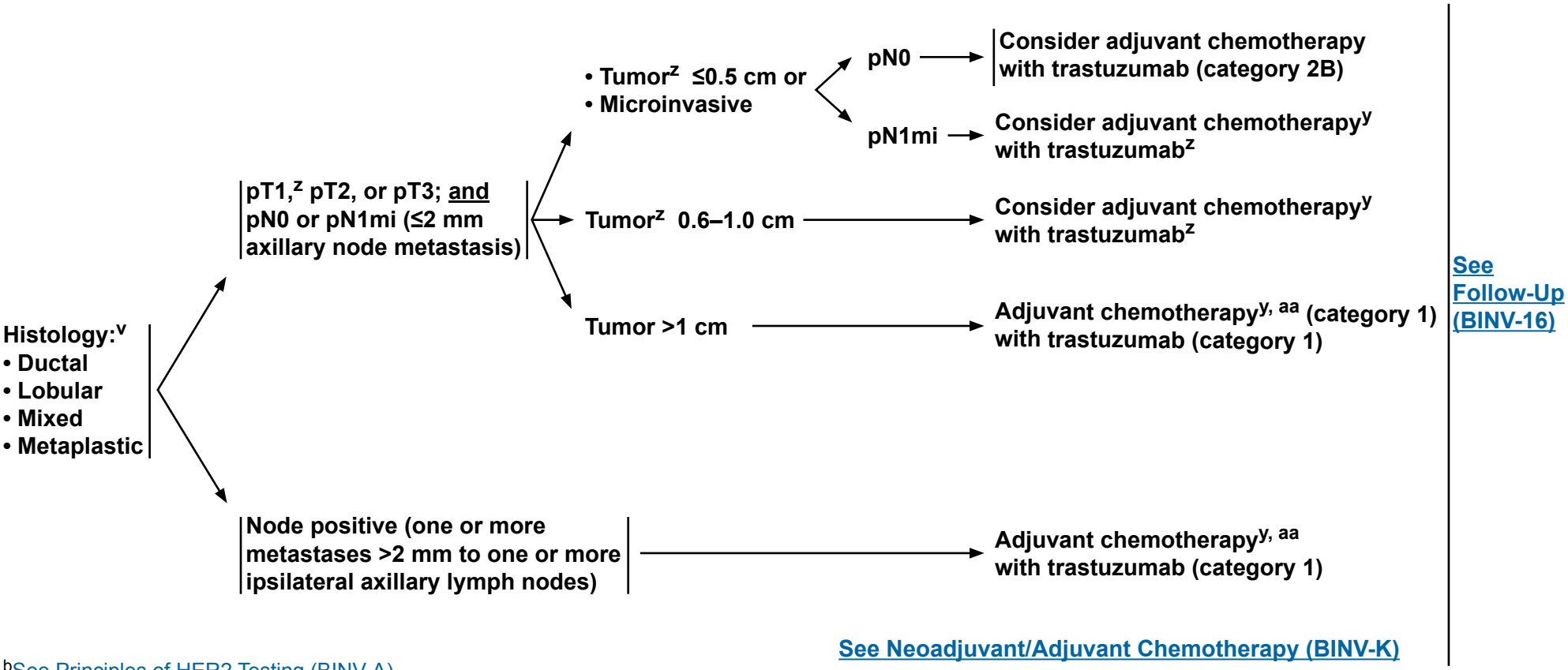
[y] There are limited data to make chemotherapy recommendations for those >70 y old. Treatment should be individualized with consideration of comorbid conditions.

[bb] The 21-gene RT-PCR assay recurrence score can be considered in select patients with 1–3 involved ipsilateral axillary lymph nodes to guide the addition of combination chemotherapy to standard hormone therapy. A retrospective analysis of a prospective randomized trial suggests that the test is predictive in this group similar to its performance in node-negative disease.

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



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

[v] 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.

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

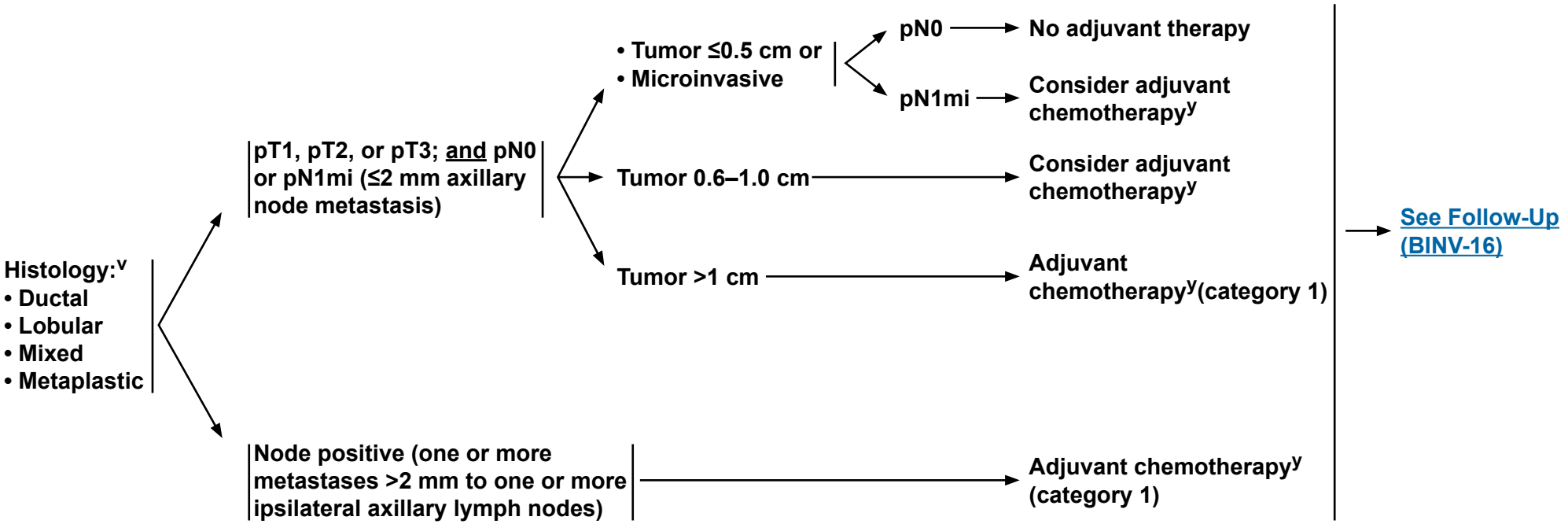
[z] The prognosis of patients with T1a and T1b tumors that are node negative is uncertain even when HER2 is amplified or overexpressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of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

[aa] A pertuzumab-containing regimen can be administered to patients with greater than or equal to T2 or greater than or equal to N1, HER2-positive, early-stage breast cancer.

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



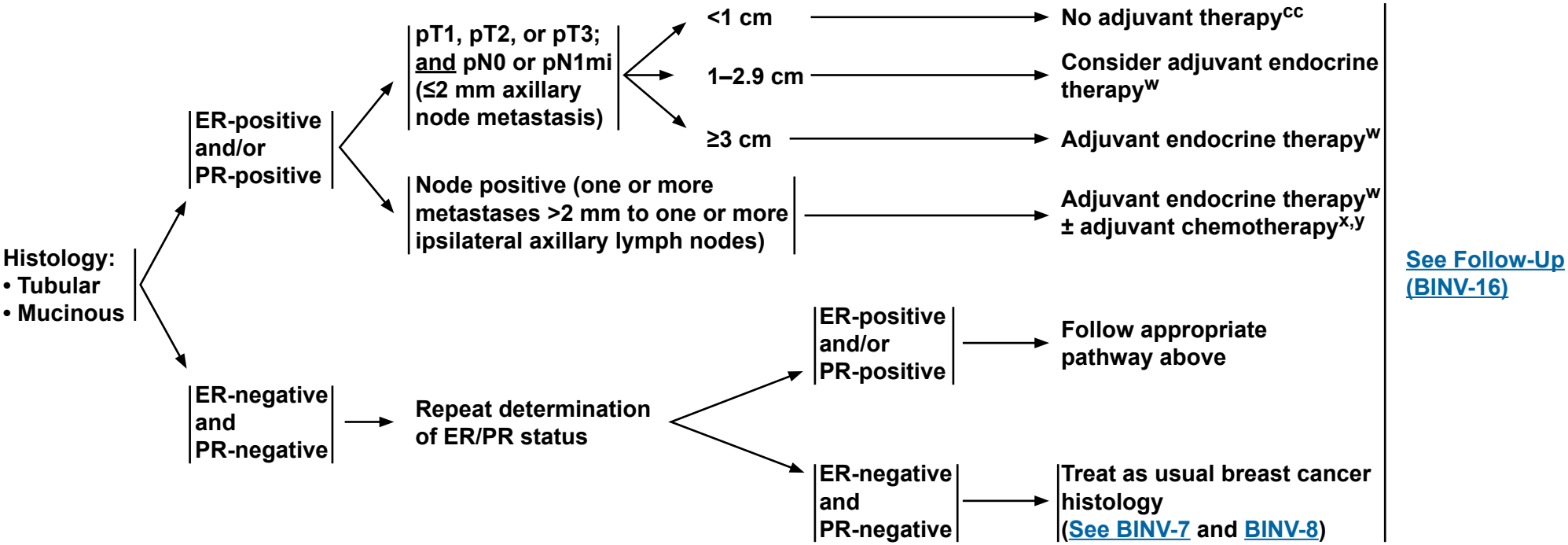
See Neoadjuvant/Adjuvant Chemotherapy (BINV-K)

[b] See Principles of HER2 Testing (BINV-A).
[v] 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.
[y] There are limited data to make chemotherapy recommendations for those >70 y old. Treatment should be individualized with consideration of comorbid conditions.

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SYSTEMIC ADJUVANT TREATMENT - FAVORABLE HISTOLOGIES



See Adjuvant Endocrine Therapy (BINV-J) and Neoadjuvant/Adjuvant Chemotherapy (BINV-K)

[w]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.

[x]Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable.

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

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

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Preoperative Systemic Therapy 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[dd]

WORKUP

- **History and physical exam**
- **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]**
- **Genetic counseling if patient is high risk for hereditary breast cancer[c]**
- **Breast MRI[d] (optional), with special consideration for mammographically occult tumors**
- **Fertility counseling if premenopausal[e]**

Consider systemic staging (particularly if signs and symptoms are present):[f]

- **Chest diagnostic CT**
- **Abdominal ± pelvic diagnostic CT or MRI**
- **Bone scan or sodium fluoride PET/CT[g] (category 2B)**
- **FDG PET/CT[h,i] (optional, category 2B)**

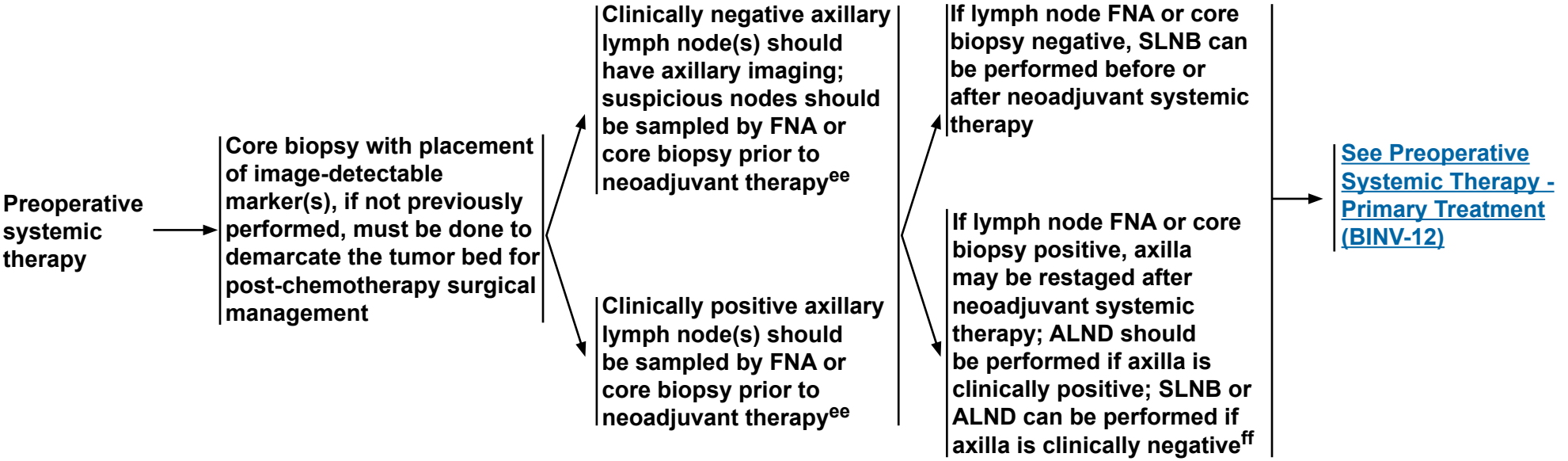
See Preoperative Systemic Therapy Breast and Axillary Evaluation (BINV-11)

[a]The panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. http://www.cap.org.
[b]See Principles of HER2 Testing (BINV-A).
[c]See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.
[d]See Principles of Dedicated Breast MRI Testing (BINV-B).
[e]See Fertility and Birth Control (BINV-C).
[f]Routine systemic staging is not indicated for early breast cancer in the absence of symptoms.
[g]If FDG PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component, bone scan or sodium fluoride PET/CT may not be needed.
[h]FDG PET/CT can be performed at the same time as diagnostic CT. The use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.
[i]FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.
[dd]In cases where breast-conserving surgery may not be possible but patient will need chemotherapy, neoadjuvant treatment remains an acceptable option.

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Preoperative Systemic Therapy Breast and Axillary Evaluation



Surgical resection → See Locoregional Treatment of Clinical Stage I, IIA, or IIB Disease or T3, N1, M0 (BINV-3)

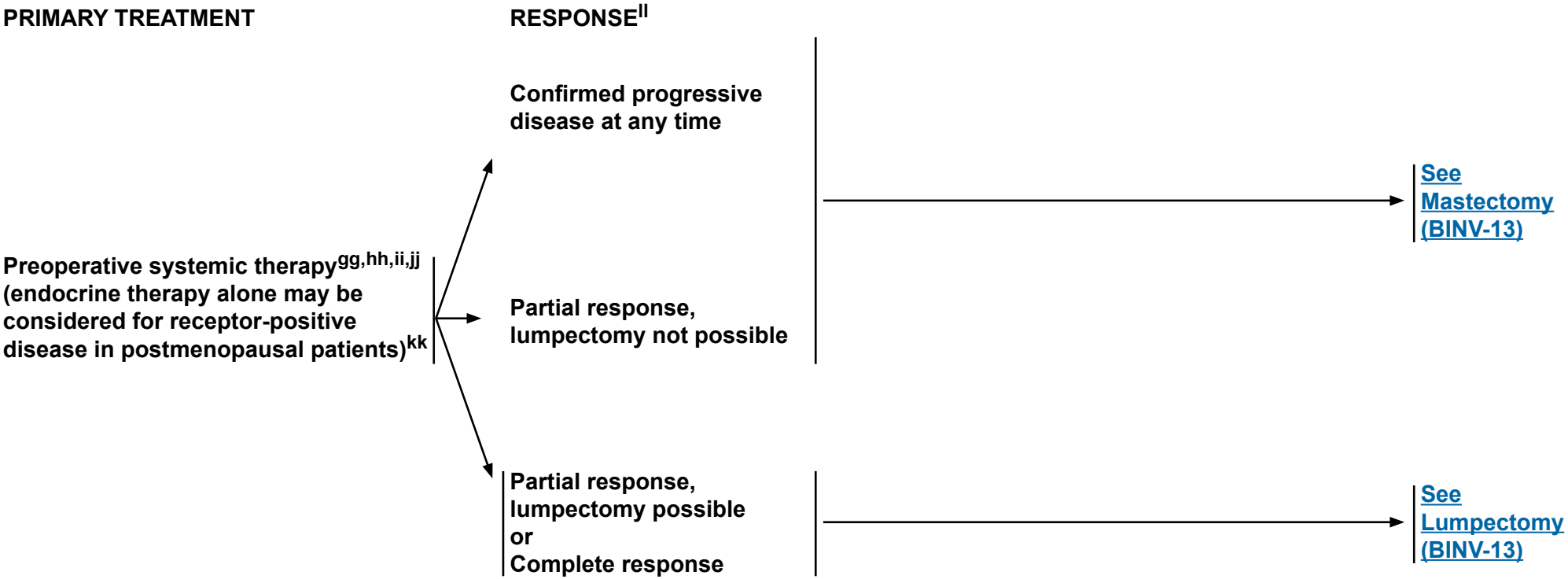
[ee]Marking of sampled axillary nodes with a tattoo or clip should be considered to permit verification that the biopsy-positive lymph node has been removed at the time of definitive surgery.

[ff]Among patients shown to be node-positive prior to neoadjuvant systemic therapy, SLNB has a >10% false-negative rate when performed after neoadjuvant systemic therapy. This rate can be improved by marking biopsied lymph nodes to document their removal, using dual tracer, and by removing more than 2 sentinel nodes.

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Preoperative Systemic Therapy Guideline (Stage IIA-IIIA)



[gg]A number of chemotherapy regimens have activity in the preoperative setting. In general, those chemotherapy regimens recommended in the adjuvant setting may be considered in the preoperative setting. See Neoadjuvant/Adjuvant Chemotherapy (BINV-K). If treated with endocrine therapy, an aromatase inhibitor is preferred for postmenopausal women.

[hh]Patients with HER2-positive tumors should be treated with preoperative systemic therapy incorporating trastuzumab for at least 9 weeks of preoperative therapy. See Neoadjuvant/Adjuvant Chemotherapy (BINV-K).

[ii]A pertuzumab-containing regimen may be administered preoperatively to patients with greater than or equal to T2 or greater than or equal to N1, HER2-positive breast cancer.

[jj] Administration of all chemotherapy prior to surgery is preferred. See Neoadjuvant/Adjuvant Chemotherapy (BINV-K).

[kk]See Definition of Menopause (BINV-L).

[ll]The accurate assessment of in-breast tumor or regional lymph node response to preoperative chemotherapy is difficult, and should include physical examination and performance of imaging studies that were abnormal at the time of initial tumor staging. Selection of imaging methods prior to surgery should be determined by the multidisciplinary team.

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Preoperative Systemic Therapy Guideline

LOCAL TREATMENT

ADJUVANT TREATMENT

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

→

- **Complete planned chemotherapy regimen course if not completed preoperatively plus endocrine treatment if ER-positive and/or PR-positive (sequential chemotherapy followed by endocrine therapy).**
- **Adjuvant radiation therapy[p] post-mastectomy is based on prechemotherapy tumor characteristics as per BINV-3**
  and
  Endocrine therapy if ER-positive and/or PR-positive[x] (category 1)
- **Complete up to one year of trastuzumab therapy if HER2-positive (category 1). May be administered concurrently with radiation therapy[p] and with endocrine therapy if indicated.**

See Adjuvant Endocrine Therapy (BINV-J)

Lumpectomy with surgical axillary staging.[j,mm] If sentinel lymph node biopsy performed prechemotherapy and negative findings, may omit axillary lymph node staging
See BINV-11

→

- **Complete planned chemotherapy regimen course if not completed preoperatively plus endocrine treatment if ER-positive and/or PR-positive (sequential chemotherapy followed by endocrine therapy).**
- **Adjuvant radiation therapy[p] post-lumpectomy based on prechemotherapy tumor characteristics as per BINV-2**
  and
  Endocrine therapy if ER-positive and/or PR-positive[x] (category 1)
- **Complete up to one year of trastuzumab therapy if HER2-positive (category 1). May be administered concurrently with radiation therapy[p] and with endocrine therapy if indicated.**

See Adjuvant Endocrine Therapy (BINV-J)

→ **See Surveillance/ Follow-up (BINV-16)**

[j] See Surgical Axillary Staging (BINV-D).
[p] See Principles of Radiation Therapy (BINV-I).
[x] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable.
[mm] Axillary staging following preoperative systemic therapy may include sentinel node biopsy or level I/II dissection. Level I/II dissection should be done for patients who were proven node-positive prior to neoadjuvant therapy (category 2B).

Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol 2013;14(7):609-18. Epub 2013/05/21.
Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA 2013;310(14):1455-61. Epub 2013/10/09.

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LOCALLY ADVANCED INVASIVE BREAST CANCER (NON-INFLAMMATORY)

CLINICAL STAGE | **WORKUP**

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

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

Stage IIIC
Any T, N3, M0

- **History and physical exam**
- **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]**
- **Genetic counseling if patient is at high risk for hereditary breast cancer[c]**
- **Breast MRI[d] (optional), with special consideration for mammographically occult tumors**
- **Fertility counseling if premenopausal[e]**

Consider systemic staging (particularly if signs and symptoms are present):

- **Chest diagnostic CT**
- **Abdominal ± pelvic diagnostic CT or MRI**
- **Bone scan or sodium fluoride PET/CT[g] (category 2B)**
- **FDG PET/CT[h,i] (optional, category 2B)**

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

See Preoperative Systemic Therapy (BINV-15)

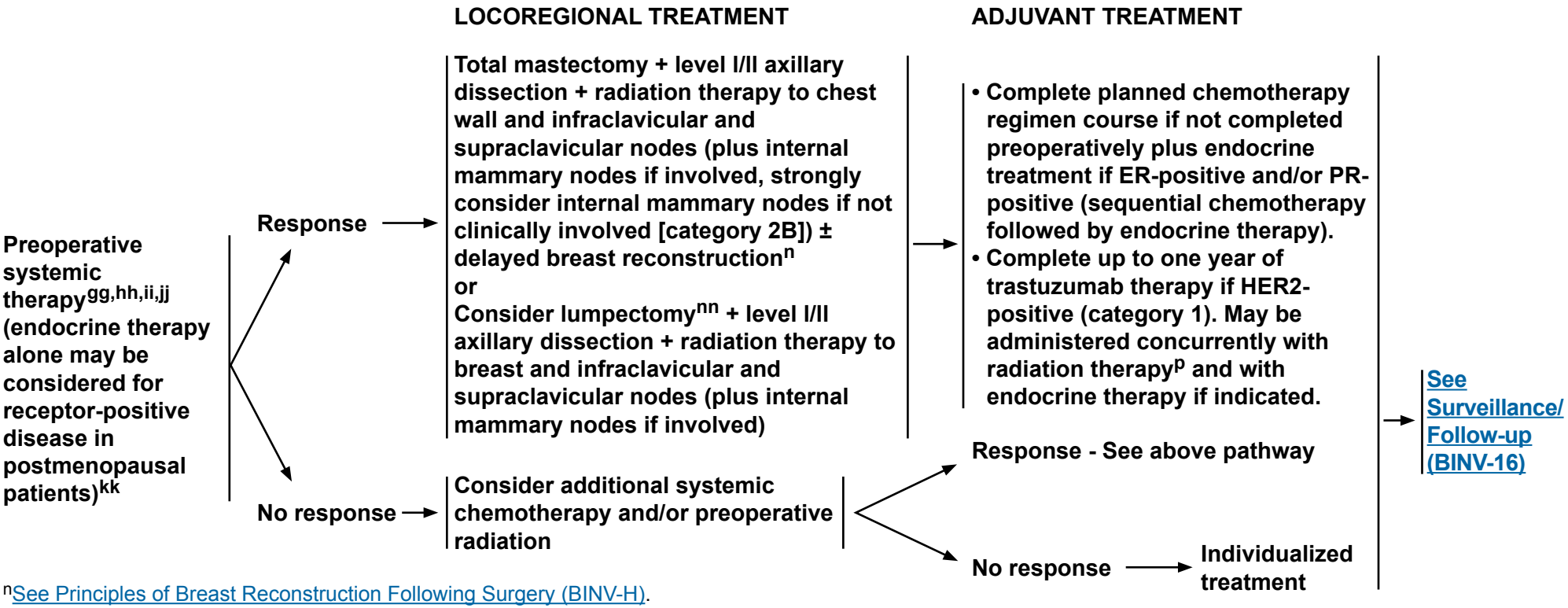
[a]The panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. http://www.cap.org.
[b]See Principles of HER2 Testing (BINV-A).
[c]See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.
[d]See Principles of Dedicated Breast MRI Testing (BINV-B).
[e]See Fertility and Birth Control (BINV-C).

[g]If FDG PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component, bone scan or sodium fluoride PET/CT may not be needed.
[h]FDG PET/CT can be performed at the same time as diagnostic CT. The use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.
[i]FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.

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PREOPERATIVE SYSTEMIC THERAPY FOR LOCALLY ADVANCED INVASIVE BREAST CANCER (NON-INFLAMMATORY)



[n] See Principles of Breast Reconstruction Following Surgery (BINV-H).
[p] See Principles of Radiation Therapy (BINV-I).
[gg] A number of chemotherapy regimens have activity in the preoperative setting. In general, those chemotherapy regimens recommended in the adjuvant setting may be considered in the preoperative setting. See Neoadjuvant/Adjuvant Chemotherapy (BINV-K). If treated with endocrine therapy, an aromatase inhibitor is preferred for postmenopausal women.
[hh] Patients with HER2-positive tumors should be treated with preoperative systemic incorporating trastuzumab for at least 9 weeks of preoperative therapy See Neoadjuvant/Adjuvant Chemotherapy (BINV-K).
[ii] A pertuzumab-containing regimen may be administered preoperatively to patients with greater than or equal to T2 or greater than or equal to N1, HER2-positive breast cancer.
[jj] Admistration of all chemotherapy prior to surgery is preferred.
[kk] See Definition of Menopause (BINV-L).
[nn] For patients with skin and/or chest wall involvement (T4 non-inflammatory) prior to neoadjuvant therapy, breast conservation may be performed in carefully selected patients based on a multidisciplinary assessment of local recurrence risk. In addition to standard contraindications to breast conservation (see BINV-G), exclusion criteria for breast conservation include: inflammatory (T4d) disease before neoadjuvant therapy and incomplete resolution of skin involvement after neoadjuvant therapy.

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SURVEILLANCE/FOLLOW-UP

- **History and physical exam 1–4 times per year as clinically appropriate for 5 y, then annually.**
- **Educate, monitor, and refer for lymphedema management**
- **Mammography every 12 mo**
- **In the absence of clinical signs and symptoms suggestive of recurrent disease, there is no indication for laboratory or imaging studies for metastases screening**
- **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[oo]**
- **Assess and encourage adherence to adjuvant endocrine therapy**
- **Evidence suggests that active lifestyle and achieving and maintaining an ideal body weight (20–25 BMI) may lead to optimal breast cancer outcomes**
- **See NCCN Guidelines for Survivorship**

→ See Recurrent Disease (BINV-17)

[oo]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. Optimal duration of bisphosphonate therapy has not been established. Factors to consider for duration of anti-osteoporosis therapy include bone mineral density, response to therapy, and risk factors for continued bone loss or fracture. Women treated with a bisphosphonate should undergo a dental examination with preventive dentistry prior to the initiation of therapy, and should take supplemental calcium and vitamin D.

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RECURRENT/STAGE IV DISEASE

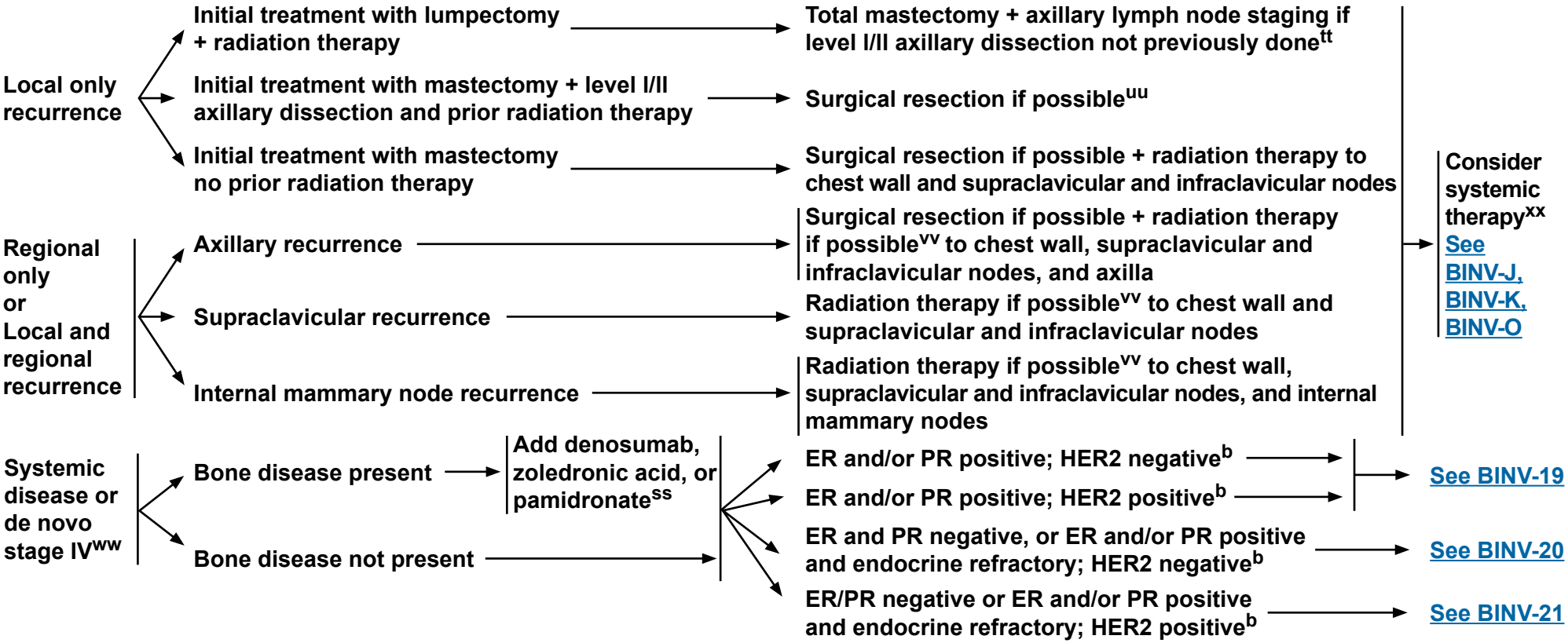
CLINICAL STAGE	WORKUP
Recurrent or Stage IV disease →	• History and physical exam • CBC, platelets • Liver function tests and alkaline phosphatase • Chest diagnostic CT • Abdominal ± pelvic diagnostic CT or MRI • Brain MRI if suspicious CNS symptoms • Bone scan or sodium fluoride PET/CT[g] (category 2B) • FDG PET/CT[i,pp] (optional, category 2B) • X-rays of symptomatic bones and long and weight-bearing bones abnormal on bone scan • First recurrence of disease should be biopsied • Determination of tumor ER/PR and HER2 status on metastatic site[b,qq,rr] • Genetic counseling if patient is high risk for hereditary breast cancer[c] → See Systemic Treatment of Recurrent or Stage IV Disease (BINV-18)

[b] See Principles of HER2 Testing (BINV-A).
[c] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.
[g] If FDG PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component, bone scan or sodium fluoride PET/CT may not be needed.
[i] FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.
[pp] FDG PET/CT can be performed at the same time as diagnostic CT. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.
[qq] 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 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, older age).
[rr] In clinical situations where a biopsy cannot safely be obtained but the clinical evidence is strongly supportive of recurrence, treatment may commence based on the ER/PR/HER2 status of the primary tumor.

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SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE



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

[ss] Denosumab, zoledronic acid, or pamidronate (all with calcium and vitamin D supplementation) should be given (category 1) in addition to chemotherapy or endocrine therapy if bone metastasis is present, expected survival is ≥3 months, and renal function is adequate. Patients should undergo a dental examination with preventive dentistry prior to initiation of this therapy. The optimal schedule for zoledronic acid is monthly x 12, then quarterly.

[tt] In women with a local breast recurrence after breast-conserving surgery who had a prior sentinel node biopsy (SNB), a repeat SNB may be technically possible. The accuracy of repeat SNB is unproven, and the prognostic significance of repeat SNB after mastectomy is unknown and its use is discouraged.

[uu] If not technically resectable, consider systemic therapy to best response, then resect if possible.

[vv] The decision to use radiation therapy to treat locoregional recurrence must factor in any prior radiation to the area and the risk of late normal tissue toxicity from the sum of the prior and planned radiation courses.

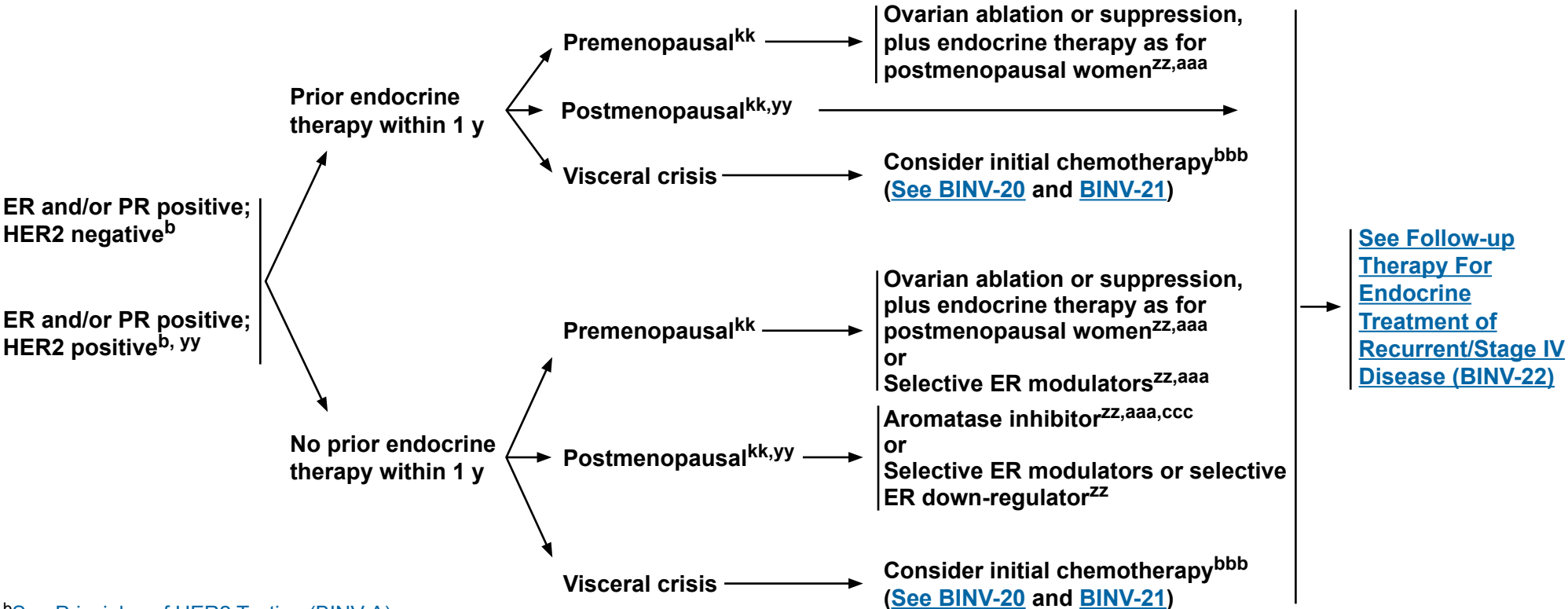
[ww] The role and timing of surgical removal of the primary in patients presenting with de novo stage IV disease is the subject of ongoing investigations.

[xx] For additional information see the Discussion section (MS-46).

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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).

[kk] See Definition of Menopause (BINV-L).

[yy] Limited studies document a progression-free survival advantage of adding trastuzumab or lapatinib to aromatase inhibition in postmenopausal patients with ER-positive, HER2-positive disease. However, no overall survival advantage has been demonstrated.

[zz] See Endocrine Therapy for Recurrent or Stage IV Disease (BINV-M).

[aaa] It is unclear that women presenting at time of initial diagnosis with metastatic disease will benefit from the performance of palliative local breast surgery and/or radiation therapy. Generally this palliative local therapy should be considered only after response to initial systemic therapy.

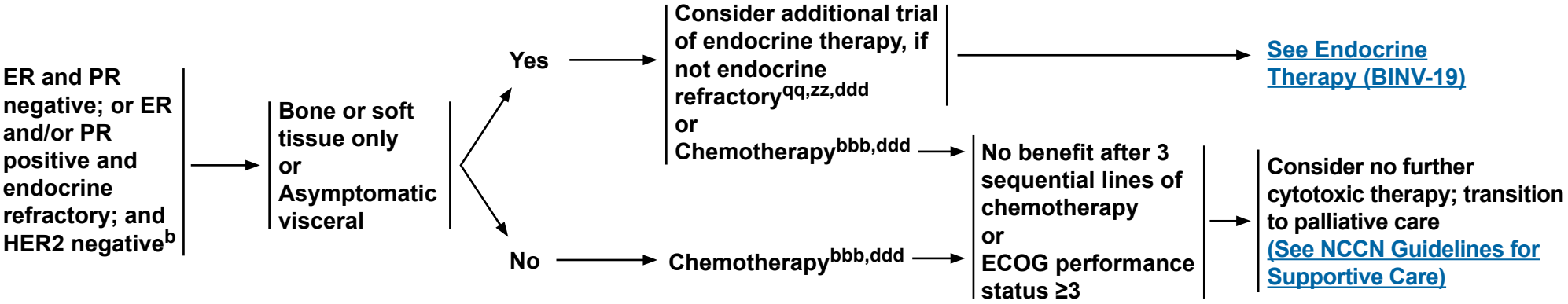
[bbb] See Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-N).

[ccc] A single study (S0226) in women with hormone receptor-positive breast cancer and no prior chemotherapy, biological therapy, or endocrine therapy for metastatic disease demonstrated that the addition of fulvestrant to anastrozole resulted in prolongation of time to progression. Subset analysis suggested that patients without prior adjuvant tamoxifen and more than 10 years since diagnosis experienced the greatest benefit. Two studies with similar design (FACT and SOFEA) demonstrated no advantage in time to progression with the addition of fulvestrant to anastrozole.

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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

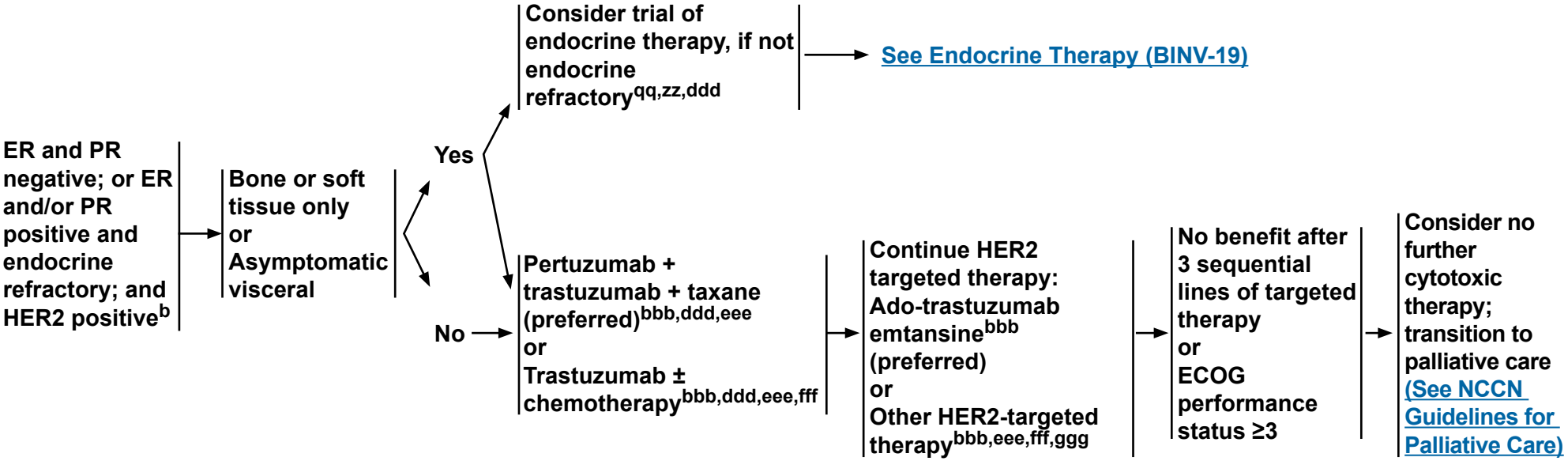


[b] See Principles of HER2 Testing (BINV-A).
[qq] False-negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy may be considered in patients with non-visceral or asymptomatic 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, older age).
[zz] See Endocrine Therapy for Recurrent or Stage IV Disease (BINV-M).
[bbb] See Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-N).
[ddd] See Principles of Monitoring Metastatic Disease (BINV-O).

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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; and HER2 POSITIVE



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

[qq] 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, older age).

[zz] See Endocrine Therapy for Recurrent or Stage IV Disease (BINV-M).

[bbb] See Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-N).

[ddd] See Principles of Monitoring Metastatic Disease (BINV-O).

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

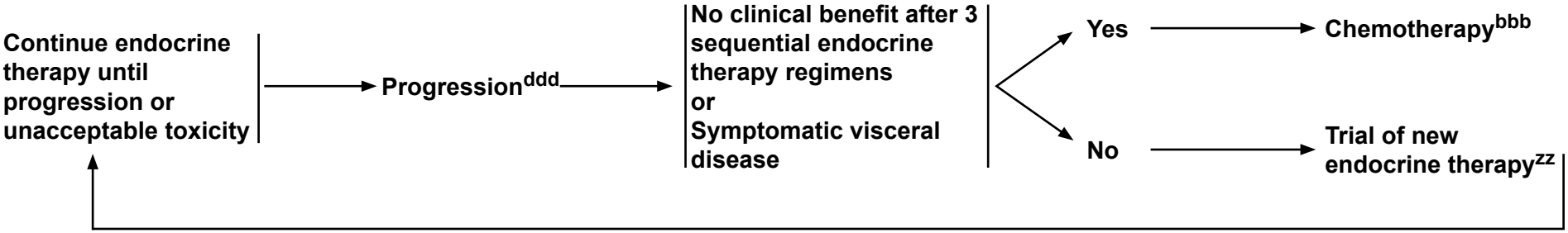
[fff] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

[ggg] Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.

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

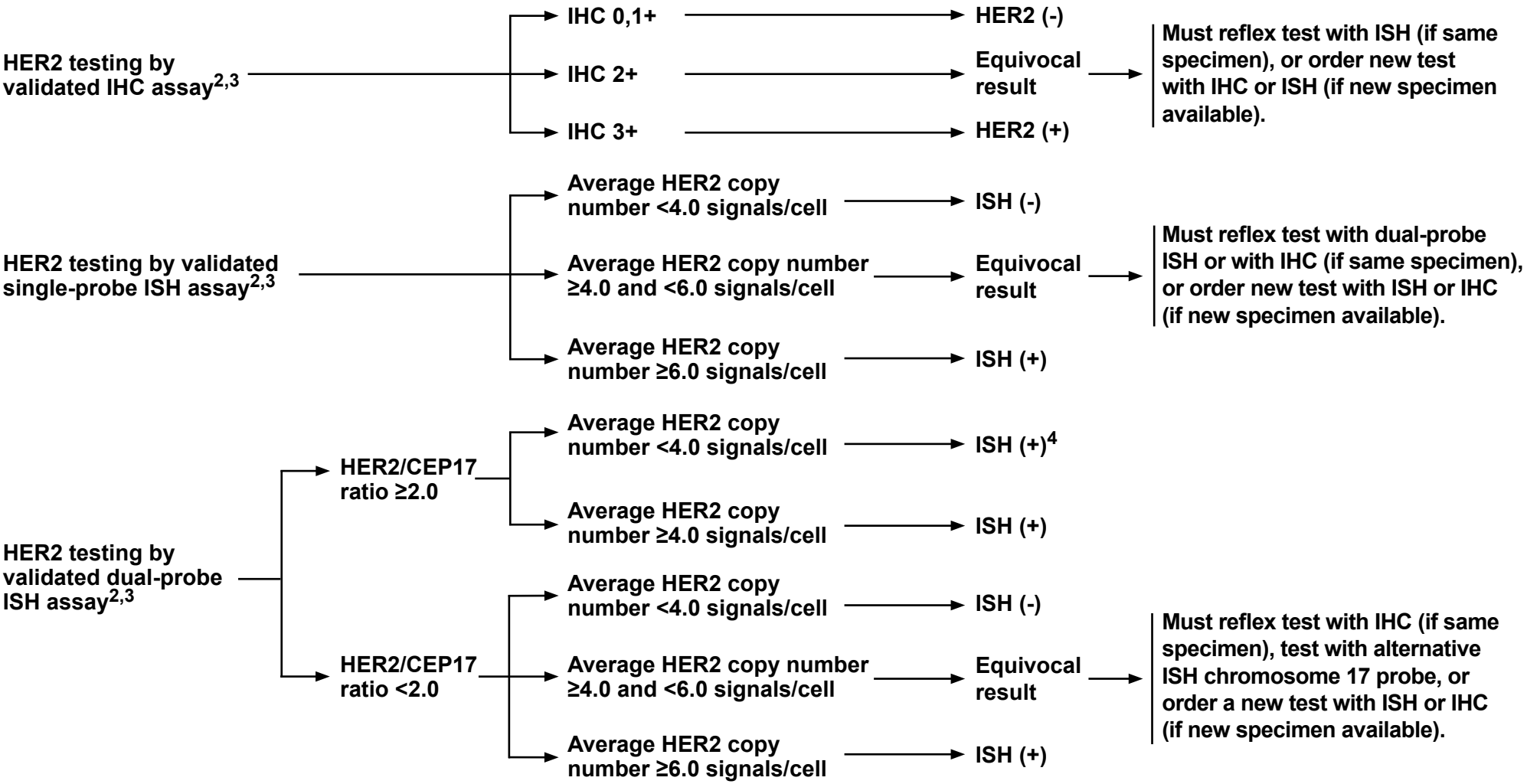


[zz] See Endocrine Therapy for Recurrent or Stage IV Disease (BINV-M).
[bbb] See Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-N).
[ddd] See Principles of Monitoring Metastatic Disease (BINV-O).

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PRINCIPLES OF HER2 TESTING[1,2]



[1]NCCN endorses the ASCO/CAP HER2 testing guideline. For additional information, see http://bit.ly/ASCO-HER2GuidelineResources.
[2]Laboratory must participate in a quality assurance accreditation program for HER2 testing. Otherwise, tissue specimen should be sent to an accredited laboratory for testing. Health care systems and providers must cooperate to ensure the highest quality testing.
[3]Evidence from trastuzumab adjuvant trials show that HER2 testing by ISH or IHC have similar utility to predict clinical benefit from HER2-targeted therapy.
[4]See ASCO/CAP HER2 Guideline Data Supplement 2E (available at http://www.asco.org/sites/www.asco.org/files/final_her2_testing_ds_10-3-13.pdf) for more information on these rare scenarios.

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PRINCIPLES OF DEDICATED BREAST MRI TESTING

See NCCN Guidelines for Breast Cancer Screening and Diagnosis 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 high-level data to demonstrate that the use of MRI to facilitate local therapy decision-making improves local recurrence or survival.[1]**
- **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 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.**
- **False-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.**
- **The utility of MRI in follow-up screening of women with prior breast cancer is undefined. It should generally be considered only in those whose lifetime risk of a second primary breast cancer is greater than 20% based on models largely dependent on family history, such as in those with the risk associated with inherited susceptibility to breast cancer.**

[1]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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FERTILITY AND BIRTH CONTROL

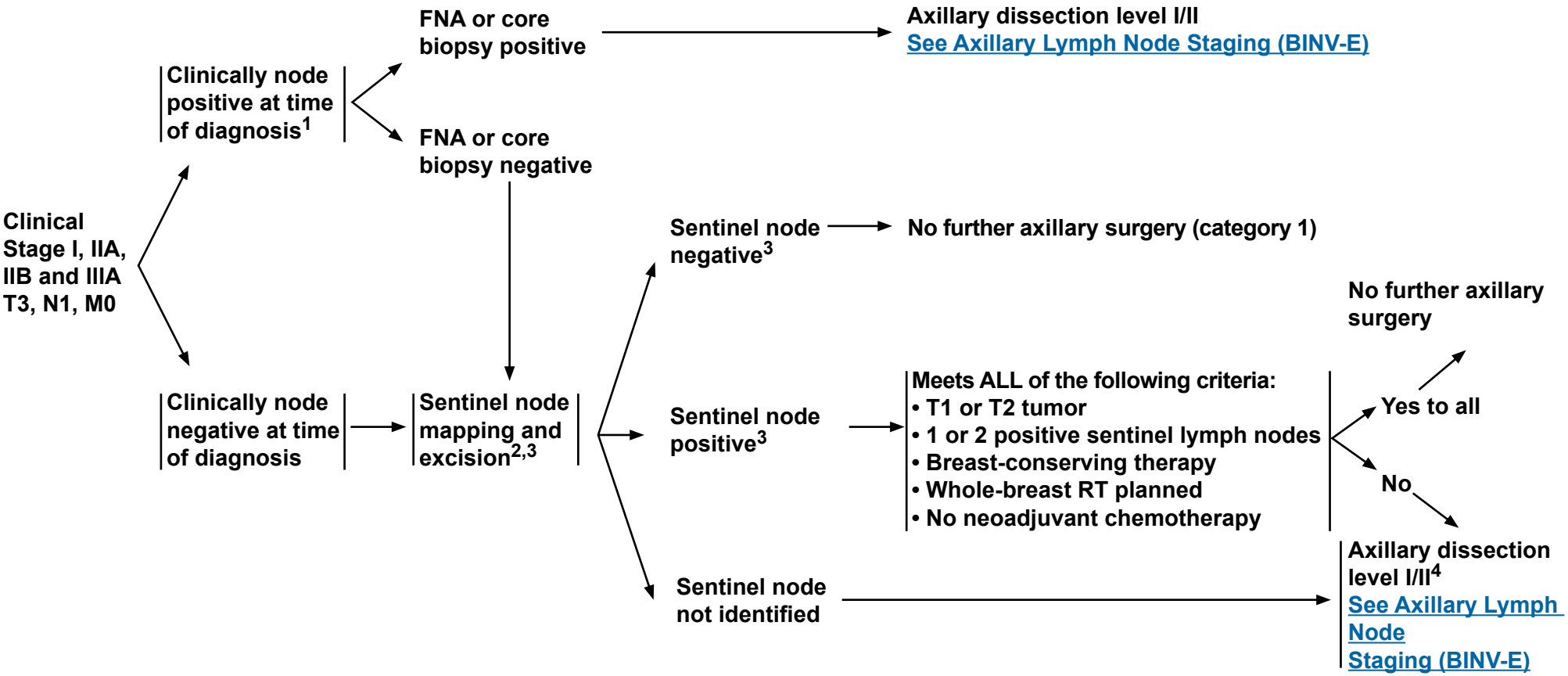
See NCCN Guidelines for Adolescent and Young Adult Oncology

- All premenopausal patients should be informed about the potential impact of chemotherapy on fertility and asked about their desire for potential future pregnancies. Patients who may desire future pregnancies should be referred to fertility specialists before chemotherapy.
- Although amenorrhea frequently occurs during or after chemotherapy, it appears that the majority of women younger than 35 y resume menses within 2 y of finishing adjuvant chemotherapy.
- Menses and fertility are not necessarily linked. Absence of regular menses, particularly if the patient is taking tamoxifen, does not necessarily imply lack of fertility. Conversely, the presence of menses does not guarantee fertility. There are limited data regarding continued fertility after chemotherapy.
- Patients should not become pregnant during treatment with radiation therapy, chemotherapy, or endocrine therapy.
- Although data are limited, hormone-based birth control is discouraged regardless of the hormone receptor status of the patient's cancer.
- Alternative methods of birth control include intrauterine devices (IUDs), barrier methods, or, for patients with no intent of future pregnancies, tubal ligation or vasectomy for the partner.
- Randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with ER-negative tumors may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea.
- Breast feeding following breast-conserving cancer treatment is not contraindicated. However, the quantity and quality of breast milk produced by the breast conserved may not be sufficient or may be lacking some of the nutrients needed. Breast feeding during active treatment with chemotherapy and endocrine therapy is not recommended.
- Smaller historical experiences in patients with ER-positive disease have reported conflicting results with regard to the protective effect of GnRH agonist therapy on fertility.

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SURGICAL AXILLARY STAGING - STAGE I, IIA, IIB and IIIA T3, N1, M0



[1]Consider pathologic confirmation of malignancy in clinically positive nodes using ultrasound-guided FNA or core biopsy in determining if a patient needs axillary lymph node dissection.
[2]Sentinel lymph node mapping injections may be peritumoral, subareolar, or subdermal. However, only peritumoral injections map to the internal mammary lymph node(s).
[3]Sentinel node involvement is defined by multilevel node sectioning with hematoxylin and eosin (H&E) staining. Cytokeratin immunohistochemistry (IHC) may be used for equivocal cases on H&E. Routine cytokeratin IHC to define node involvement is not recommended in clinical decision making.
[4]For patients with clinically negative axillae who are undergoing mastectomy and for whom radiation therapy is planned, axillary radiation may replace axillary dissection level I/II for regional control of disease.

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Return to Locoregional Treatment (BINV-2)

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AXILLARY LYMPH NODE STAGING

In the absence of definitive data demonstrating superior survival, the performance of axillary lymph node dissection 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, for the elderly, or those with serious comorbid conditions.

Level III dissection to the thoracic inlet should be performed only in cases with gross disease in level II.
In the absence of gross disease in level II nodes, lymph node dissection should include tissue inferior to the axillary vein from the latissimus dorsi muscle laterally to the medial border of the pectoralis minor muscle (Level I/II).

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-D).

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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. The NCCN Panel accepts the definition of a negative margin as "No ink on the tumor," from the 2014 Society of Surgical Oncology-American Society for Radiation Oncology Consensus Guidelines on Margins.[1] 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.

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 (EIC).[2] For these patients, the use of a higher radiation boost dose to the tumor bed should be considered. A boost to the tumor bed is recommended in patients at higher risk (age <50 or high-grade disease, or patients with focally postive margins). Typical doses are 10–16 Gy at 2 Gy/fx.

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]Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol. 2014 May 10;32(14):1507-15.
[2]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:

- **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:

- **Prior radiation therapy to the chest wall or breast; knowledge of doses and volumes prescribed is essential.**
- **Active connective tissue disease involving the skin (especially scleroderma and lupus)**
- **Tumors >5 cm (category 2B)**
- **Diffusely positive pathologic margins[1]**
- **Women with a known or suspected genetic predisposition to breast cancer:**
  - **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 Guidelines for Breast Cancer Risk Reduction).

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

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PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

- **Breast reconstruction may be an option for any woman receiving surgical treatment for breast cancer. All women undergoing breast cancer treatment should be educated about breast reconstructive options as adapted to their individual clinical situation. However, breast reconstruction should not interfere with the appropriate surgical management of the cancer. The process of breast reconstruction should not govern the timing or the scope of appropriate surgical treatment for this disease. The availability of or the practicality of breast reconstruction should not result in the delay or refusal of appropriate surgical intervention.**

- **An evaluation of the likely cosmetic outcome of lumpectomy should be performed prior to surgery. Oncoplastic techniques for breast conservation can extend breast-conserving surgical options in situations where the resection itself would likely yield an unacceptable cosmetic outcome. Application of these procedures may reduce the need for mastectomy and reduce the chances of secondary surgery for re-excision while minimizing breast deformity. Patients should be informed of the possibility of positive margins and potential need for secondary surgery, which could include re-excision segmental resection, or could require mastectomy with or without loss of the nipple. Oncoplastic procedures can be combined with surgery on the contralateral unaffected breast to minimize long-term asymmetry.**

- **For mastectomy, the possibility of reconstruction should be discussed and a preoperative evaluation of reconstructive options should be considered. Surgical options for breast reconstruction following mastectomy include:**
  - **Procedures that incorporate breast implants (ie, tissue expander placement followed by implant placement, immediate implant placement)**
  - **Procedures that incorporate autologous tissue transplantation (ie, pedicled TRAM flap, fat grafting, various microsurgical flaps from the abdomen, back, buttocks, and thigh)**
  - **Procedures that incorporate both breast implants and autologous tissue transplantation (eg, latissimus dorsi flaps)**

- **Breast reconstruction following mastectomy can commence at the same time as mastectomy ("immediate") or at some time following the completion of cancer treatment ("delayed"). In many cases, breast reconstruction involves a staged approach requiring more than one procedure such as:**
  - **Surgery on the contralateral breast to improve symmetry**
  - **Revision surgery involving the breast and/or donor site**
  - **Nipple and areola reconstruction and tattoo pigmentation**

- **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 perform a resection that achieves appropriate surgical margins. Post-mastectomy radiation should still be applied in cases treated by skin-sparing mastectomy following the same selection criteria as for standard mastectomy.**

- **Immediate reconstruction is contraindicated in the setting of mastectomy for inflammatory breast cancer (IBC) due to the high risk of recurrence, aggressive nature of the disease, and consequent need to proceed expeditiously to postoperative radiotherapy for local control without any potential delay. As skin-sparing mastectomy has not yet been demonstrated to be safe for IBC there is also a need to resect currently or previously involved skin at the time of mastectomy. Thus, there is no advantage to immediate reconstruction in this setting.**

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PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

- In general, the nipple-areolar complex (NAC) is sacrificed with skin-sparing mastectomy for cancer therapy. However, NAC-sparing procedures may be an option in cancer patients who are carefully selected by experienced multidisciplinary teams. Retrospective data support the use of NAC-sparing procedures for breast cancer therapy with low nipple-involvement rates and low local-recurrence rates for early-stage, biologically favorable (eg, Nottingham grade 1 or 2, node-negative, HER2/neu negative, no lymphovascular invasion), invasive cancers and/or DCIS that is peripherally located in the breast (>2 cm from nipple). Nipple margin assessment is mandatory, and the nipple margin should be clearly designated. Evidence of nipple involvement such as Paget's disease or bloody nipple discharge contraindicates nipple preservation.

- In the previously radiated patients, the use of tissue expanders/implants is relatively contraindicated. Tissue expansion of irradiated skin can result in a significantly increased risk of capsular contracture, malposition, poor cosmesis, implant exposure, and failed reconstruction. In the setting of previous radiation, autologous tissue reconstruction is the preferred method of breast reconstruction.

- While noninflammatory, locally advanced breast cancer is not an absolute contraindication to immediate reconstruction, post-mastectomy radiation should still be applied regardless of the reconstruction approach:
  - When post-mastectomy radiation is required and autologous tissue reconstruction is planned, reconstruction is either delayed until after the completion of radiation therapy, or it can be initiated at the time of mastectomy with tissue expander placement followed by autologous tissue reconstruction. While some experienced breast cancer teams have employed protocols in which immediate tissue reconstructions are followed by radiation therapy, it is generally preferred that the radiation therapy precede the placement of the autologous tissue, because of reported loss in reconstruction cosmesis (category 2B).
  - When implant reconstruction is planned in a patient requiring radiation therapy, a staged approach with immediate tissue expander placement followed by implant placement is preferred. Surgery to exchange the tissue expanders with permanent implants can be performed prior to radiation or after completion of radiation therapy. Immediate placement of an implant in patients requiring postoperative radiation has an increased rate of capsular contracture, malposition, poor cosmesis, and implant exposure.

- Reconstruction selection is based on an assessment of cancer treatment, patient body habitus, obesity, smoking history, comorbidities, and patient concerns. Smoking and obesity increase the risk of complications for all types of breast reconstruction whether with implant or flap. Smoking and obesity are therefore considered a relative contraindication to breast reconstruction and patients should be made aware of increased rates of wound healing complications and partial or complete flap failure among smokers and obese patients.

- 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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PRINCIPLES OF RADIATION THERAPY

Whole Breast Radiation:
Target definition includes the majority of the breast tissue, and is best done by both clinical assessment and CT-based treatment planning. A uniform dose distribution and minimal normal tissue toxicity are the goals and can be accomplished using compensators such as wedges, forward planning using segments, intensity-modulated radiation therapy (IMRT), respiratory gating, or prone positioning. The breast should receive a dose of 45–50 Gy in 23-25 fractions or 40–42.5 Gy in 15–16 fractions (short course is preferred). A boost to the tumor bed is recommended in patients at higher risk (age <50 and high-grade disease). 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 that 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 anatomy 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 50–50.4 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 are given 5 days per week. Based on the modern post-mastectomy radiation randomized trials and other recent studies, consider including the internal mammary lymph nodes when delivering regional nodal irradiation. CT treatment planning should be utilized in all cases where radiation therapy is delivered to the internal mammary lymph node field.

Accelerated Partial Breast Irradiation (APBI):
Preliminary studies of APBI suggest that rates of local control in selected patients with early-stage breast cancer may be comparable to those treated with standard whole breast RT. However, compared to standard whole breast radiation, several recent studies document an inferior cosmetic outcome with APBI. Follow-up is limited and studies are ongoing. Patients are encouraged to participate in clinical trials. If not trial eligible, per the consensus statement from the American Society for Radiation Oncology (ASTRO), patients who may be suitable for APBI are women 60 y and older who are not carriers of *BRCA 1/2* mutation treated with primary surgery for a unifocal T1N0 ER-positive cancer. Histology should be infiltrating ductal or a favorable ductal subtype and not associated with EIC or LCIS, and margins should be negative. Thirty-four Gy in 10 fractions delivered twice per day with brachytherapy or 38.5 Gy in 10 fractions delivered twice per day with external beam photon therapy is prescribed to the tumor bed. Other fractionation schemes are currently under investigation.

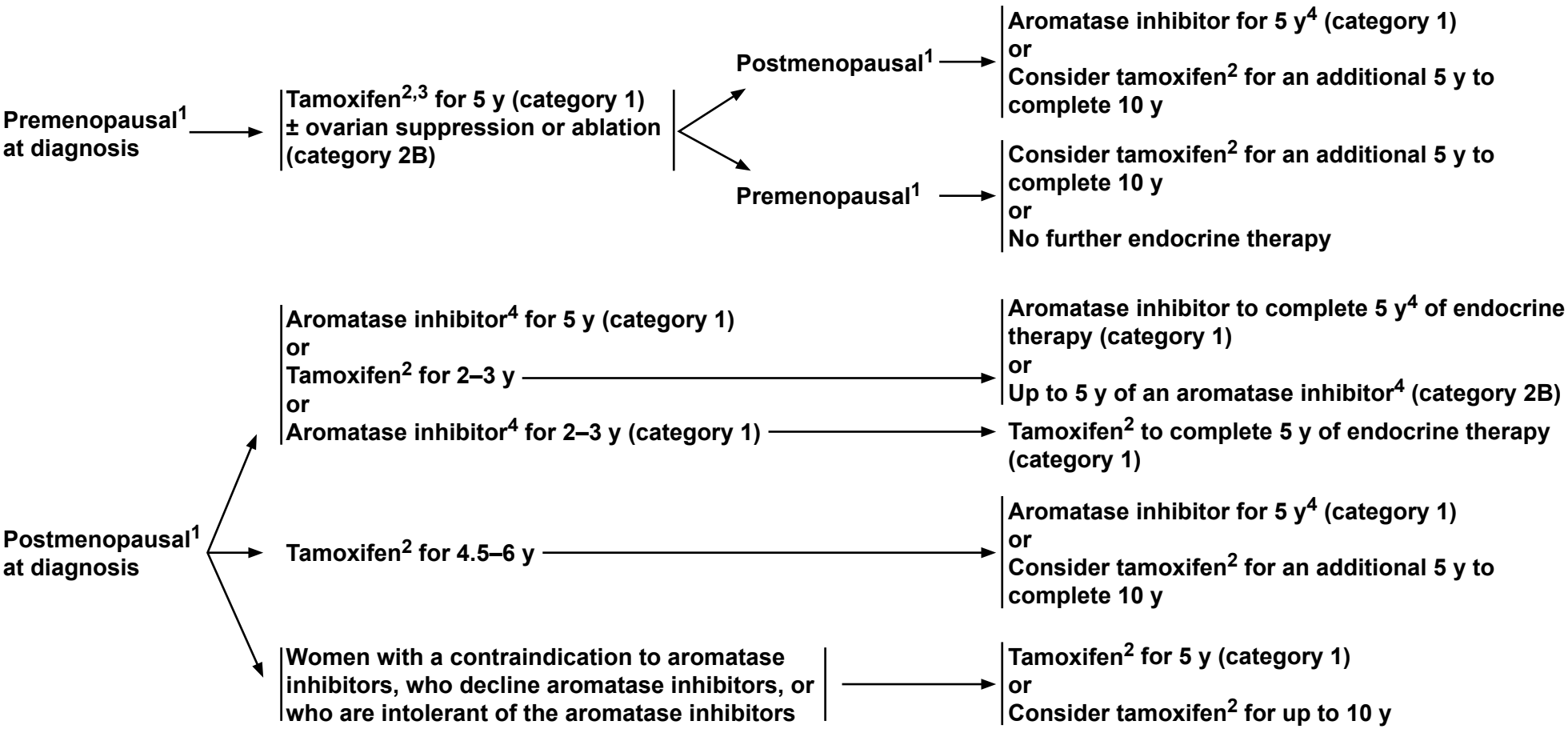
Optimizing Delivery of Individual Therapy:
It is important to individualize delivery of radiation therapy and considerations such as patient positioning (ie, prone vs. supine) during administration of radiation therapy.

Neoadjuvant Chemotherapy:
Indications for radiation therapy and fields of treatment should be based on the worst stage pretreatment or post-treatment tumor characteristics in patients treated with neoadjuvant chemotherapy.

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ADJUVANT ENDOCRINE THERAPY



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

[2] Some SSRIs like fluoxetine and paroxetine decrease the formation of endoxifen, 4-OH tamoxifen, and active metabolites of tamoxifen, and may impact its efficacy. Caution is advised about coadministration of these drugs with tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. At this time, based on current data the panel recommends against CYP2D6 testing for women being considered for tamoxifen therapy. Coadministration of strong inhibitors of CYP2D6 should be used with caution.

[3] Aromatase inhibitor for 5 y + ovarian suppression may be considered as an alternative option based on SOFT and TEXT clinical trial outcomes. Pagani O, Regan M, Walley B, et al. Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer. N Engl J Med 2014; 371:107-118.

[4] The panel believes the three selective aromatase inhibitors (ie, anastrozole, letrozole, exemestane) have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant and neoadjuvant settings. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.

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NEOADJUVANT/ADJUVANT CHEMOTHERAPY[1,2,3,4]

Regimens for HER2-negative disease (all category 1)[5]

Preferred regimens:

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

Other regimens:

- **Dose-dense AC (doxorubicin/cyclophosphamide)**
- **AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B)**
- **FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide)**
- **FEC/CEF (cyclophosphamide/epirubicin/fluorouracil)**
- **CMF (cyclophosphamide/methotrexate/fluorouracil)**
- **AC followed by docetaxel every 3 weeks**
- **AC followed by weekly paclitaxel**
- **EC (epirubicin/cyclophosphamide)**
- **FEC/CEF followed by T (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel) or (fluorouracil/epirubicin/cyclophosphamide followed by weekly paclitaxel)**
- **FAC followed by T (fluorouracil/doxorubicin/cyclophosphamide followed by weekly paclitaxel)**
- **TAC (docetaxel/doxorubicin/cyclophosphamide)**

[1]Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to non-anthracycline-based regimens in patients with HER2-positive tumors.
[2]Randomized clinical trials demonstrate that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.
[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 endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy.
[5]The regimens listed for HER2-negative disease are all category 1 when used in the adjuvant setting.

Regimens for HER2-positive disease[6,7,8]

Preferred regimens:

- **AC followed by T + trastuzumab ± pertuzumab[9] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab ± pertuzumab, various schedules)**
- **TCH (docetaxel/carboplatin/trastuzumab) ± pertuzumab**

Other regimens:

- **AC followed by docetaxel + trastuzumab ± pertuzumab[9]**
- **Docetaxel + cyclophosphamide + trastuzumab**
- **FEC followed by docetaxel + trastuzumab + pertuzumab[9]**
- **FEC followed by paclitaxel + trastuzumab + pertuzumab[9]**
- **Paclitaxel + trastuzumab[10]**
- **Pertuzumab + trastuzumab + docetaxel followed by FEC[9]**
- **Pertuzumab + trastuzumab + paclitaxel followed by FEC[9]**

[6]In patients with HER2-positive and axillary node-positive breast cancer, trastuzumab should be incorporated into the adjuvant therapy (category 1). Trastuzumab should also be considered for patients with HER2-positive node-negative tumors ≥1 cm (category 1).
[7]Trastuzumab should optimally be given concurrently with paclitaxel as part of the AC followed by paclitaxel regimen, and should be given for one year total duration.
[8]A pertuzumab-containing regimen can be administered to patients with greater than or equal to T2 or greater than or equal to N1, HER2-positive, early-stage breast cancer. Patients who have not received a neoadjuvant pertuzumab-containing regimen can receive adjuvant pertuzumab.
[9]Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[10]Paclitaxel + trastuzumab may be considered for patients with low-risk stage I, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.

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DOSING SCHEDULES FOR COMBINATIONS FOR HER2-NEGATIVE DISEASE: PREFERRED REGIMENS

OTHER REGIMENS LISTED ON NEXT PAGE

Dose-dense AC followed by paclitaxel chemotherapy[1]
- **Doxorubicin 60 mg/m² IV day 1**
- **Cyclophosphamide 600 mg/m² IV day 1**

Cycled every 14 days for 4 cycles.
(All cycles are with myeloid growth factor support)
Followed by:
- **Paclitaxel 175 mg/m² by 3 h IV infusion day 1**

Cycled every 14 days for 4 cycles.

Dose-dense AC followed by weekly paclitaxel chemotherapy[1]
- **Doxorubicin 60 mg/m² IV day 1**
- **Cyclophosphamide 600 mg/m² IV day 1**

Cycled every 14 days for 4 cycles.
(All cycles are with myeloid growth factor support)
Followed by:
- **Paclitaxel 80 mg/m² by 1 h IV infusion weekly for 12 wks.**

TC chemotherapy[2]
- **Docetaxel 75 mg/m² IV day 1**
- **Cyclophosphamide 600 mg/m² IV day 1**

Cycled every 21 days for 4 cycles.
(All cycles are with myeloid growth factor support)

The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and 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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DOSING SCHEDULES FOR COMBINATIONS FOR HER2-NEGATIVE DISEASE: OTHER REGIMENS

Dose-dense AC chemotherapy[1]
- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 14 days for 4 cycles.

AC chemotherapy[3]
- Doxorubicin 60 mg/m² IV on day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 days for 4 cycles.

TAC chemotherapy[4]
- Docetaxel 75 mg/m² IV day 1
- Doxorubicin 50 mg/m² IV day 1
- Cyclophosphamide 500 mg/m² IV day 1

Cycled every 21 days for 6 cycles.
(All cycles are with myeloid growth factor support)

FAC chemotherapy[5,6]
- 5-fluorouracil 500 mg/m² IV days 1 & 8 or days 1 & 4
- Doxorubicin 50 mg/m² IV day 1 (or by 72-h continuous infusion)
- Cyclophosphamide 500 mg/m² IV day 1

Cycled every 21 days for 6 cycles.

CAF chemotherapy[7]
- Cyclophosphamide 100 mg/m² PO days 1–14
- Doxorubicin 30 mg/m² IV days 1 & 8
- 5-fluorouracil 500 mg/m² IV days 1 & 8

Cycled every 28 days for 6 cycles.

CEF chemotherapy[8]
- Cyclophosphamide 75 mg/m² PO days 1–14
- Epirubicin 60 mg/m² IV days 1 & 8
- 5-fluorouracil 500 mg/m² IV days 1 & 8

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

CMF chemotherapy[9]
- Cyclophosphamide 100 mg/m² PO days 1–14
- Methotrexate 40 mg/m² IV days 1 & 8
- 5-fluorouracil 600 mg/m² IV days 1 & 8

Cycled every 28 days for 6 cycles.

AC followed by docetaxel chemotherapy[10]
- Doxorubicin 60 mg/m² IV on day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 days for 4 cycles.
Followed by:
- Docetaxel 100 mg/m² IV on day 1

Cycled every 21 days for 4 cycles.

AC followed by weekly paclitaxel[11]
- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² 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.

EC chemotherapy[12]
- Epirubicin 100 mg/m² IV day 1
- Cyclophosphamide 830 mg/m² IV day 1

Cycled every 21 days for 8 cycles.

FEC followed by docetaxel chemotherapy[13]
- 5-fluorouracil 500 mg/m² IV day 1
- Epirubicin 100 mg/m² IV day 1
- Cyclophosphamide 500 mg/m² IV day 1

Cycled every 21 days for 3 cycles.
Followed by:
- Docetaxel 100 mg/m² IV day 1

Cycled every 21 days for 3 cycles.

FEC followed by weekly paclitaxel[14]
- 5-fluorouracil 600 mg/m² IV day 1
- Epirubicin 90 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 days for 4 cycles.
Followed by:
Paclitaxel 100 mg/m² IV infusion weekly for 8 wks.

FAC followed by weekly paclitaxel
- 5-fluorouracil 500 mg/m² IV days 1 & 8 or days 1 & 4
- Doxorubicin 50 mg/m² IV day 1 (or by 72-h continuous infusion)
- Cyclophosphamide 500 mg/m² IV day 1

Cycled every 21 days for 6 cycles.
Followed by:
- Paclitaxel 80 mg/m² by 1 h IV infusion weekly for 12 wks.

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DOSING SCHEDULE FOR COMBINATIONS FOR HER2-POSITIVE DISEASE: PREFERRED REGIMENS

AC followed by T chemotherapy with trastuzumab[15]
- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² 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 21 days 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.

AC followed by T chemotherapy with trastuzumab + pertuzumab
- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 days for 4 cycles.
Followed by:
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Paclitaxel 80 mg/m² IV days 1, 8, and 15

Cycled every 21 days for 4 cycles
- Trastuzumab 6 mg/kg IV day 1

Cycled every 21 days to complete 1 y of trastuzumab therapy
Cardiac monitoring at baseline, 3, 6, and 9 mo.

Dose-dense AC followed by paclitaxel chemotherapy with trastuzumab[16]
- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 14 days for 4 cycles.
Followed by:
- Paclitaxel 175 mg/m² by 3 h IV infusion day 1

Cycled every 14 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 21 days 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.

TCH chemotherapy[17]
- Docetaxel 75 mg/m² IV day 1
- Carboplatin AUC 6 IV day 1

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

Followed by:
- Trastuzumab 2 mg/kg IV for 17 wks

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

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

TCH chemotherapy + pertuzumab[18]
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Docetaxel 75 mg/m² IV day 1
- Carboplatin AUC 6 IV day 1

Cycled every 21 days for 6 cycles
Followed by:
- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y 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 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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DOSING SCHEDULE FOR COMBINATIONS FOR HER2-POSITIVE DISEASE: OTHER REGIMENS

AC followed by docetaxel chemotherapy with trastuzumab[17]
- 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:
- Docetaxel 100 mg/m^2 IV day 1

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

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

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

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

AC followed by docetaxel chemotherapy with trastuzumab and pertuzumab
- 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:
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Docetaxel 75–100 mg/m^2 IV day 1

Cycled every 21 days for 4 cycles
Followed by:
- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

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

Docetaxel/cyclophosphamide chemotherapy with trastuzumab[19]
- Docetaxel 75 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 4 cycles
With:
Trastuzumab 4 mg/kg IV wk 1
Followed by
Trastuzumab 2 mg/kg IV weekly for 11 wks
Followed by
Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy
Cardiac monitoring at baseline, 3, 6, and 9 mo.

FEC chemotherapy followed by pertuzumab + trastuzumab + docetaxel[18]
- Fluorouracil 500 mg/m^2 IV day 1
- Epirubicin 100 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 3 cycles
Followed by:
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Docetaxel 75–100 mg/m^2 IV day 1

Cycled every 21 days for 3 cycles
Followed by:
- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y 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 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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DOSING SCHEDULE FOR COMBINATIONS FOR HER2-POSITIVE DISEASE: OTHER REGIMENS (continued)

FEC chemotherapy followed by pertuzumab + trastuzumab + paclitaxel
- Fluorouracil 500 mg/m^2 IV day 1
- Epirubicin 100 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 3 cycles
Followed by:
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Paclitaxel 80 mg/m^2 IV days 1, 8, and 15

Cycled every 21 days for 3 cycles
Followed by:
- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

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

Paclitaxel + trastuzumab[20]
- Paclitaxel 80 mg/m^2 IV weekly for 12 weeks

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 21 days 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.

Pertuzumab + trastuzumab + docetaxel followed by FEC chemotherapy[21]
Neoadjuvant therapy:
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Docetaxel 75–100 mg/m^2 IV day 1

Cycled every 21 days for 4 cycles
Followed by adjuvant therapy
- Fluorouracil 600 mg/m^2 IV day 1
- Epirubicin 90 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 3 cycles
Followed by:
- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

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

Pertuzumab + trastuzumab + paclitaxel followed by FEC chemotherapy
Neoadjuvant therapy:
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Paclitaxel 80 mg/m^2 IV days 1, 8, and 15

Cycled every 21 days for 4 cycles
Followed by adjuvant therapy
- Fluorouracil 600 mg/m^2 IV day 1
- Epirubicin 90 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 3 cycles
Followed by:
- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y 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 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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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 follicle-stimulating hormone (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 LHRH 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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ENDOCRINE THERAPY FOR RECURRENT OR STAGE IV DISEASE

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

Postmenopausal Patients

- **Non-steroidal aromatase inhibitor (anastrozole, letrozole)**
- **Steroidal aromatase inactivator (exemestane)**
- **Exemestane + everolimus[1]**
- **Palbociclib + letrozole[2]**
- **Fulvestrant**
- **Tamoxifen or toremifene**
- **Megestrol acetate**
- **Fluoxymesterone**
- **Ethinyl estradiol**

[1]A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 mo or on non-steroidal AI, or any time on tamoxifen).
[2]Palbociclib in combination with letrozole may be considered as a treatment option for first-line therapy for postmenopausal patients with ER-positive, HER2-negative metastatic breast cancer.

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CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER[1]

Preferred single agents:

Anthracyclines
- Doxorubicin
- Pegylated liposomal doxorubicin

Taxanes
- Paclitaxel

Anti-metabolites
- Capecitabine
- Gemcitabine

Other microtubule inhibitors
- Vinorelbine
- Eribulin

Other single agents:
- Cyclophosphamide
- Carboplatin
- Docetaxel
- Albumin-bound paclitaxel
- Cisplatin
- Epirubicin
- Ixabepilone

Chemotherapy combinations:
- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[2]

Preferred first-line agents for HER2-positive disease:
- Pertuzumab + trastuzumab + docetaxel (category 1)[4]
- Pertuzumab + trastuzumab + paclitaxel[4]

Other first-line agents for HER2-positive disease:

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

Preferred agents for trastuzumab-exposed HER2-positive disease:
- Ado-trastuzumab emtansine (T-DM1)

Other agents for trastuzumab-exposed HER2-positive disease:
- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents[3,4]

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

[2]Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.

[3]Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

[4]Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab in the metastatic setting may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.

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DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

Preferred single agents:

Anthracyclines:

Doxorubicin
- 60–75 mg/m² IV day 1, cycled every 21 days[1]

or
- 20 mg/m² IV day 1 weekly[2]

Pegylated liposomal encapsulated doxorubicin[3]
- 50 mg/m² IV day 1

Cycled every 28 days.

Taxanes:

Paclitaxel
- 175 mg/m² IV day 1

Cycled every 21 days.[4]
or
- 80 mg/m² IV day 1 weekly[5]

Antimetabolites:

Capecitabine[6]
- 1000–1250 mg/m² PO twice daily days 1–14

Cycled every 21 days.

Gemcitabine[7]
- 800–1200 mg/m² IV days 1, 8, and 15

Cycled every 28 days.

Other microtubule inhibitors:

Vinorelbine[8]
- 25 mg/m² IV day 1 weekly

Eribulin[9]
- 1.4 mg/m² IV days 1 and 8

Cycled every 21 days.

Other single agents:

Cyclophosphamide[10]
- 50 mg PO daily on days 1–21

Cycled every 28 days.

Carboplatin[11]
- AUC 6 IV on day 1

Cycled every 21–28 days.

Docetaxel[12,13]
- 60-100 mg/m² IV day 1

Cycled every 21 days.
or
- 35 mg/m² IV weekly for 6 wks followed by a 2-week rest, then repeat[14]

Albumin-bound paclitaxel
- 100 mg/m² or 150 mg/m² IV days 1, 8, and 15

Cycled every 28 days.[15,16]
or
- 260 mg/m² IV

Cycled every 21 days.[15]

Cisplatin[17]
- 75 mg/m² IV on day 1

Cycled every 21 days.

Epirubicin[18]
- 60–90 mg/m² IV day 1

Cycled every 21 days.

Ixabepilone[19]
- 40 mg/m² IV day 1

Cycled every 21 days.

See References (BINV-N, 6 of 7)

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 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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DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

Chemotherapy combinations:

CAF chemotherapy[20]
- 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[21]
- 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.

FEC chemotherapy[22]
- 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[23]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days.

EC chemotherapy[24]
- Epirubicin 75 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days.

CMF chemotherapy[25]
- 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[26]
- 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[27]
- 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.

Gemcitabine/carboplatin[28]
- Gemcitabine 1000 mg/m^2 on days 1 & 8
- Carboplatin AUC 2 IV on days 1 & 8

Cycled every 21 days.

Paclitaxel plus bevacizumab[29]
- 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.

See References (BINV-N, 6 of 7)

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 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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DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR HER-2 POSITIVE RECURRENT OR METASTATIC BREAST CANCER

Preferred first-line agents for HER2-positive disease:

Pertuzumab + trastuzumab + docetaxel[30]
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Docetaxel 75–100 mg/m² IV day 1

Cycled every 21 days.

Pertuzumab + trastuzumab + paclitaxel[31]
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV cycled every 21 days
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV cycled every 21 days[33]
- Paclitaxel 80 mg/m² IV day 1 weekly[31]
  or
- Paclitaxel 175 mg/m² day 1 cycled every 21 days

Other first-line agents for HER2-positive disease:

Paclitaxel/carboplatin + trastuzumab[32]
- Carboplatin AUC 6 IV day 1
- Paclitaxel 175 mg/m² IV day 1

Cycled every 21 days.
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

Weekly paclitaxel/carboplatin + trastuzumab[34]
- Paclitaxel 80 mg/m² IV days 1, 8, & 15
- Carboplatin AUC 2 IV days 1, 8, & 15

Cycled every 28 days.
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

Trastuzumab + paclitaxel
- Paclitaxel
  - 175 mg/m² IV day 1 cycled every 21 days[35]
    or
  - 80–90 mg/m² IV day 1 weekly[36]
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

Trastuzumab + docetaxel
- Docetaxel
  - 80–100 mg/m² IV day 1 cycled every 21 days[37]
    or
  - 35 mg/m² IV days 1, 8, and 15 weekly[38]
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

Trastuzumab + vinorelbine[39]
- Vinorelbine
  - 25 mg/m² IV day 1 weekly
    or
  - 30–35 mg/m² IV days 1 and 8

Cycled every 21 days.
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

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DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR HER-2 POSITIVE RECURRENT OR METASTATIC BREAST CANCER

Trastuzumab + capecitabine[41]
- Capecitabine 1000–1250 mg/m^2 PO twice daily days 1–14
  cycled every 21 days
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly[35,42]
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

Preferred agents for trastuzumab-exposed HER2-positive disease:

Ado-trastuzumab emtansine (T-DM1)[43]
- 3.6 mg/kg IV day 1

Cycled every 21 days.

Other agents for trastuzumab-exposed HER2-positive disease:

Lapatinib + capecitabine[44]
- Lapatinib 1250 mg PO daily days 1–21
- Capecitabine 1000 mg/m^2 PO twice daily days 1–14

Cycled every 21 days.

Trastuzumab + capecitabine[45]
- Capecitabine 1000–1250 mg/m^2 PO twice daily days 1–14

Cycled every 21 days.
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly[35,42]
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

Trastuzumab + lapatinib[46]
- Lapatinib 1000 mg PO daily
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

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References continued on the next page

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PRINCIPLES OF MONITORING METASTATIC DISEASE

Monitoring of patient symptoms and cancer burden during treatment of metastatic breast cancer is important to determine whether the treatment is providing benefit and that the patient does not have toxicity from an ineffective therapy.

Components of Monitoring:
Monitoring includes periodic assessment of varied combinations of symptoms, physical examination, routine laboratory tests, imaging studies, and blood biomarkers where appropriate. Results of monitoring are classified as response/continued response to treatment, stable disease, uncertainty regarding disease status, or progression of disease. The clinician typically must assess and balance multiple different forms of information to make a determination regarding whether disease is being controlled and the toxicity of treatment is acceptable. Sometimes, this information may be contradictory.

Definition of Disease Progression:
Unequivocal evidence of progression of disease by one or more of these factors is required to establish progression of disease, either because of ineffective therapy or acquired resistance of disease to an applied therapy. Progression of disease may be identified through evidence of growth or worsening of disease at previously known sites of disease and/or of the occurrence of new sites of metastatic disease.

- **Findings concerning for progression of disease include:**
  - **Worsening symptoms such as pain or dyspnea**
  - **Evidence of worsening or new disease on physical examination**
  - **Declining performance status**
  - **Unexplained weight loss**
  - **Increasing alkaline phosphatase, ALT, AST, or bilirubin**
  - **Hypercalcemia**
  - **New radiographic abnormality or increase in the size of pre-existing radiographic abnormality**
  - **New areas of abnormality on functional imaging (eg, bone scan, PET/CT scan)**
  - **Increasing tumor markers (eg, CEA, CA15-3, CA27.29)[1]**

Continued on next page

[1]Rising tumor markers (eg, CEA, CA15-3, CA27.29) are concerning for tumor progression, but may also be seen in the setting of responding disease. An isolated increase in tumor markers should rarely be used to declare progression of disease. Changes in bone lesions are often difficult to assess on plain or cross-sectional radiology or on bone scan. For these reasons, patient symptoms and serum tumor markers may be more helpful in patients with bone-dominant metastatic disease.

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PRINCIPLES OF MONITORING METASTATIC DISEASE

Use of Objective Criteria for Response/Stability/Progression:

- **The most accurate assessments of disease activity typically occur when previously abnormal studies are repeated on a serial and regular basis. Generally, the same method of assessment should be used over time (eg, an abnormality found on chest CT scan should generally be monitored with repeat chest CT scans).**
- **Some non-clinically important variation in measurement of abnormalities by all serial studies is common and expected. Therefore, the use of objective and widely accepted criteria for response, stability, and progression of disease are encouraged. Such systems include the Response Evaluation Criteria In Solid Tumors (RECIST) guidelines (Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247) and the WHO criteria (Miller AB, Hoogstraten B, Staquet M, and Winkler A. Reporting results of cancer treatment. Cancer 1981;47:207-214).**
- **Studies of functional imaging, such as radionuclide bone scans and PET imaging, are particularly challenging when used to assess response. In the case of bone scans, responding disease may result in a flare or increased activity on the scan that may be misinterpreted as disease progression, especially on the first follow-up bone scan after initiating a new therapy. PET imaging is challenging because of the absence of a reproducible, validated, and widely accepted set of standards for disease activity assessment.**

Frequency of Monitoring:

The optimal frequency of repeat testing is uncertain, and is primarily based upon the monitoring strategies utilized in breast cancer clinical trials. The frequency of monitoring must balance the need to detect progressive disease, avoid unnecessary toxicity of any ineffective therapy, resource utilization, and determine cost. The following table is to provide guidance, and should be modified for the individual patient based upon sites of disease, biology of disease, and length of time on treatment. Reassessment of disease activity should be performed in patients with new or worsening signs or symptoms of disease, regardless of the time interval from previous studies.

Continued on next page

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PRINCIPLES OF MONITORING METASTATIC DISEASE

Suggested intervals of follow-up for patients with metastatic disease[1]

	Baseline prior to new therapy	Chemotherapy	Endocrine therapy	Restaging if concern for progression of disease
Symptom assessment	Yes	Prior to each cycle	Every 2–3 months	Yes
Physical examination	Yes	Prior to each cycle	Every 2–3 months	Yes
Performance status	Yes	Prior to each cycle	Every 2–3 months	Yes
Weight	Yes	Prior to each cycle	Every 2–3 months	Yes
LFTs, CBC	Yes	Prior to each cycle	Every 2–3 months	Yes
CT scan chest/abd/pelvis	Yes	Every 2–4 cycles	Every 2–6 months	Yes
Bone scan	Yes	Every 4 cycles	Every 4–6 months	Yes
PET/CT	Optional	Unknown	Unknown	Optional
Tumor markers	Optional	Optional	Optional	Optional

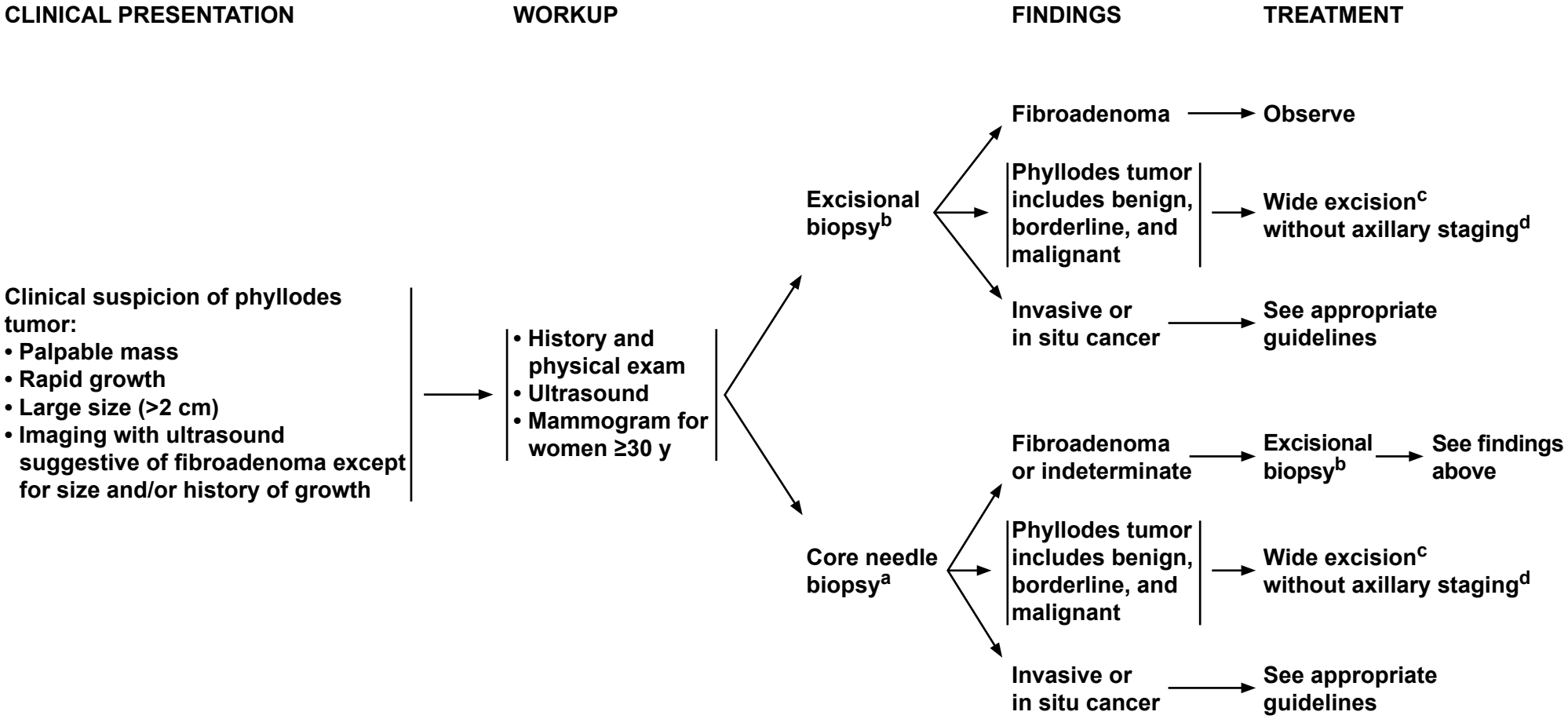
[1]In patients who have long-term stable disease, the frequency of monitoring can be reduced.

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NCCN Guidelines Version 3.2015
Phyllodes Tumor

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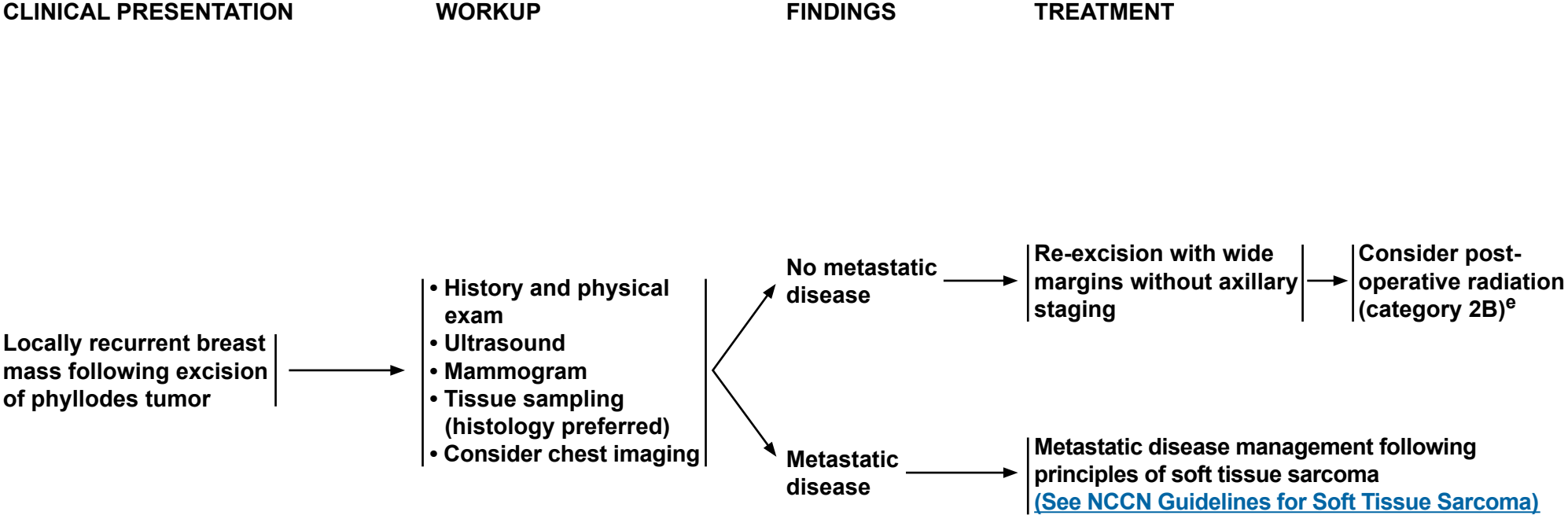


[a]FNA will not, and core biopsy may not distinguish fibroadenoma from a phyllodes tumor in most cases.
[b]Excisional biopsy includes complete mass removal, but without the intent of obtaining surgical margins.
[c]Wide excision means excision with the intention of obtaining surgical margins ≥1 cm. Narrow surgical margins are associated with heightened local recurrence risk, but are not an absolute indication for mastectomy when partial mastectomy fails to achieve margin width ≥1 cm.
[d]There are 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 mastectomy), radiation therapy may be considered following.the same principles that are applied to the treatment of soft tissue sarcoma.

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PHYLLODES TUMOR RECURRENCE



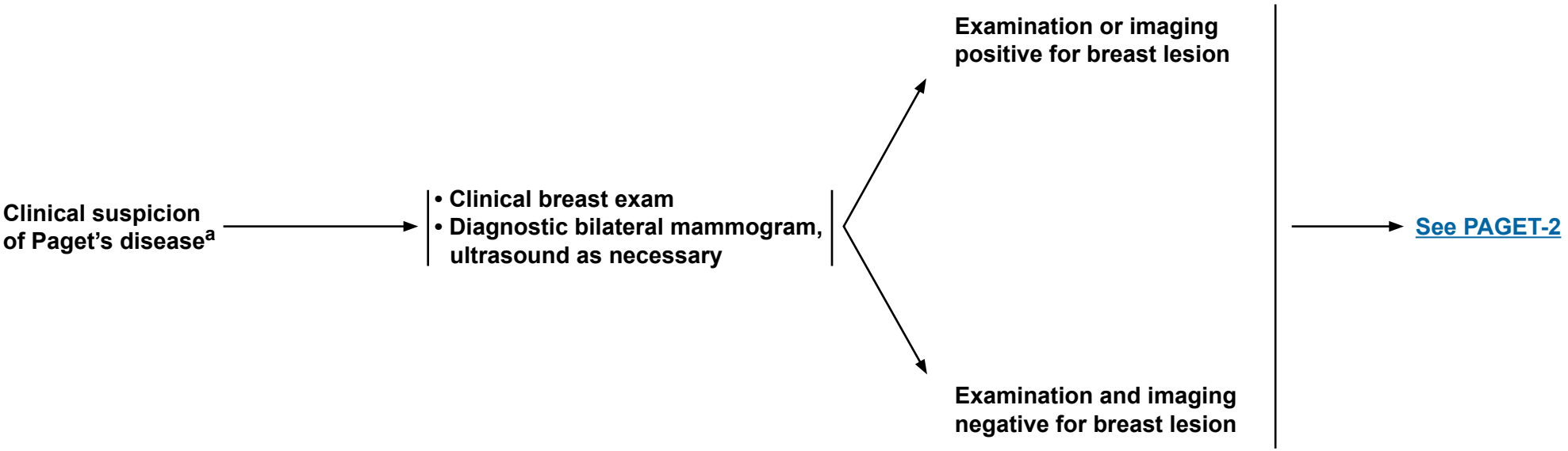
[e]There are no prospective randomized data supporting the use of radiation treatment with phyllodes tumors. However, in the setting where additional recurrence would create significant morbidity (eg, chest wall recurrence following mastectomy), radiation therapy may be considered following the same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

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CLINICAL PRESENTATION

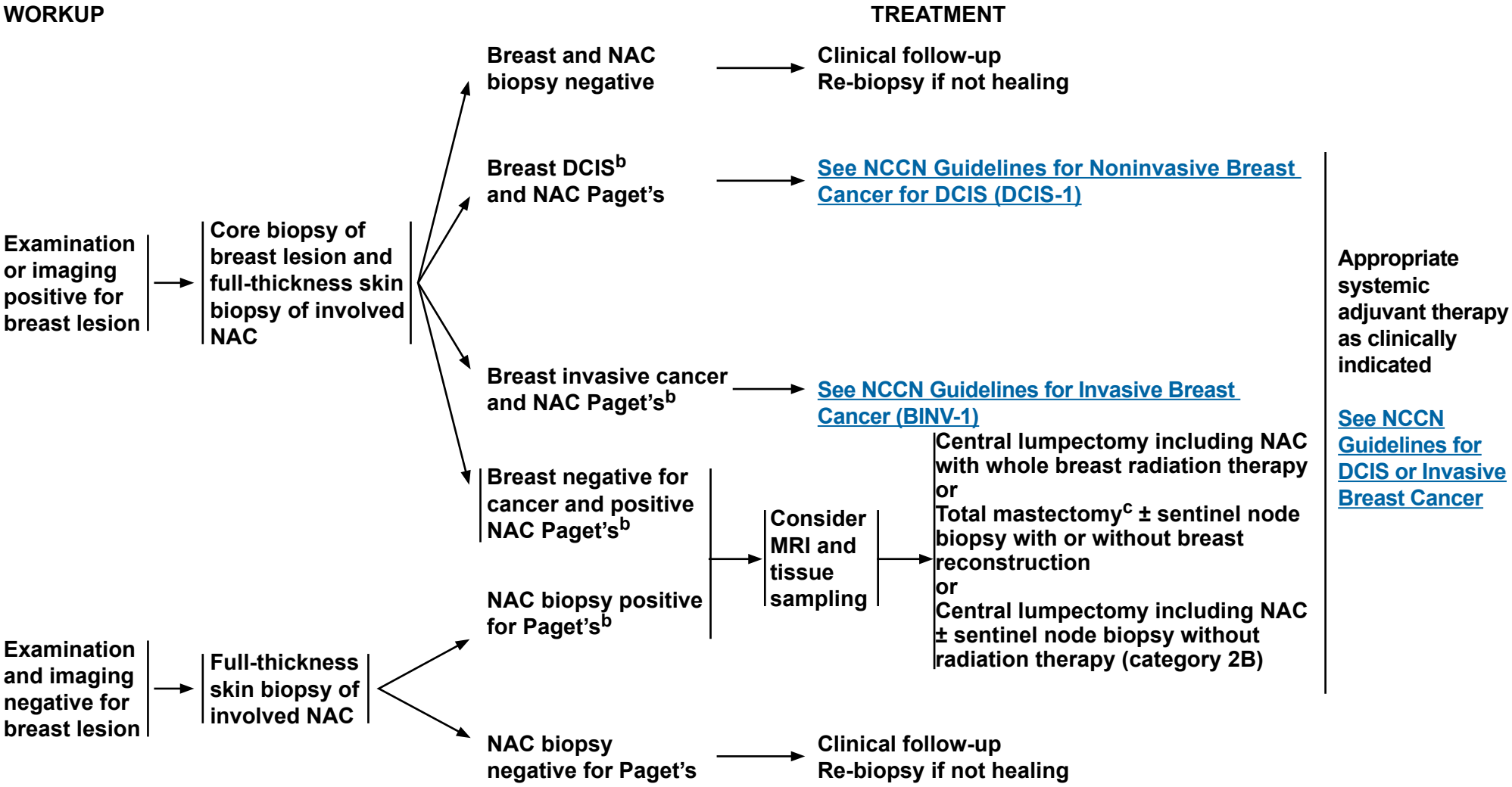
WORKUP



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

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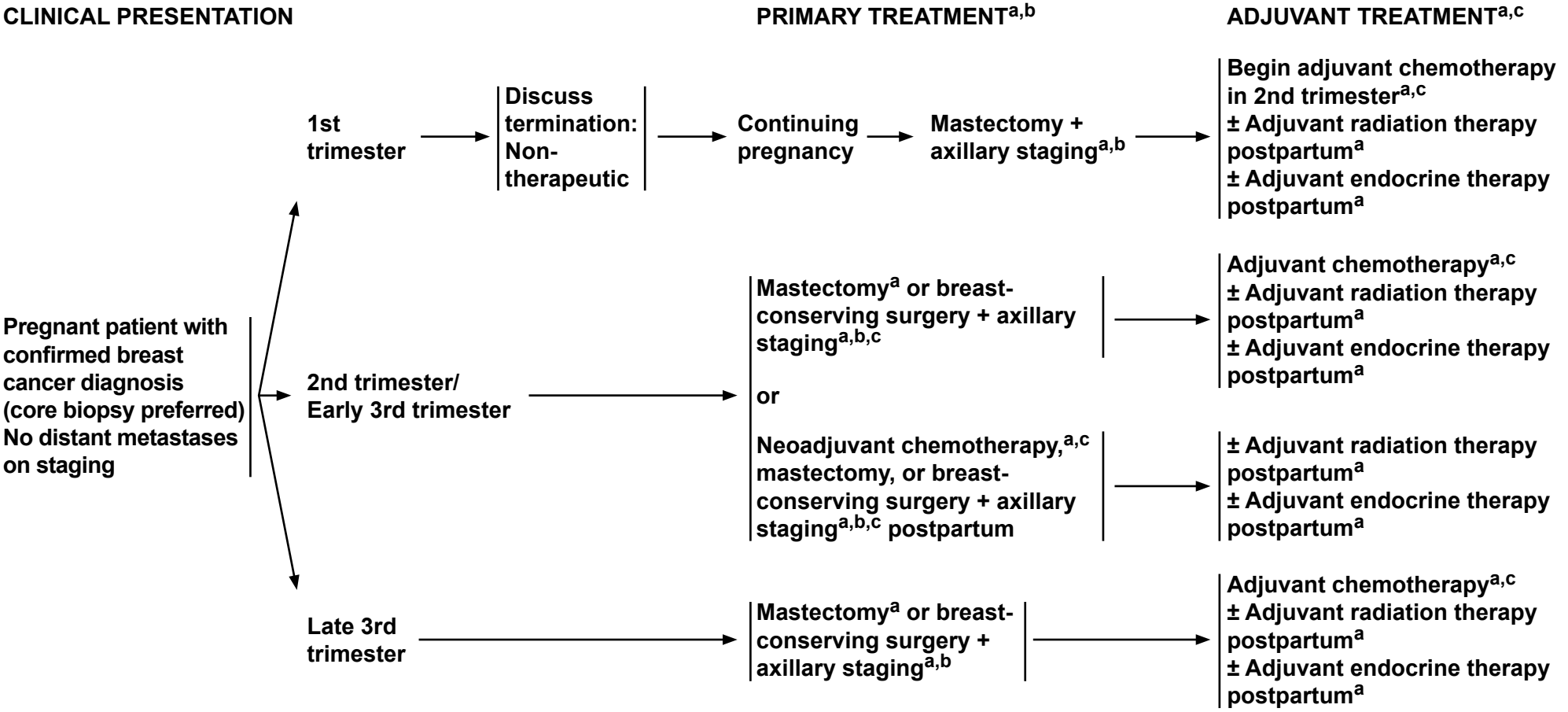
[b]To assess the extent of disease or to confirm additional disease, consider MRI. See Principles of Dedicated Breast MRI Testing (BINV-B).
[c]Mastectomy is always an option with any manifestation of Paget's disease (See Discussion section).

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NCCN Guidelines Version 3.2015
Breast Cancer During Pregnancy

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[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 (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. Considerations for postpartum chemotherapy are the same as for non-pregnancy-associated breast cancer.

[b]Use of blue dye is contraindicated in pregnancy; radiolabeled sulfur colloid appears to be safe for sentinel node biopsy in pregnancy. See Surgical Axillary Staging (BINV-D).

[c]There are insufficient safety data to recommend general use of taxanes during pregnancy. However, the use of paclitaxel weekly administration after the first trimester is acceptable if clinically indicated by disease status. The use of anti-HER2 therapy is contraindicated during pregnancy.

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NCCN Guidelines Version 3.2015
Inflammatory Breast Cancer

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CLINICAL PRESENTATION[a]

Clinical pathologic diagnosis of inflammatory breast cancer (IBC) Stage T4d, N0-N3, M0

WORKUP

- **History and physical exam by multidisciplinary team**
- **CBC, platelets**
- **Liver function tests**
- **Pathology review[b]**
- **Determination of tumor ER/PR status and HER2 status[c]**
- **Bilateral diagnostic mammogram, ultrasound as necessary**
- **Breast MRI (optional)**
- **Fertility counseling if premenopausal[d]**
- **Bone scan or sodium fluoride PET/CT (category 2B)[e]**
- **Chest/abdominal/pelvic diagnostic CT (category 2B)**
- **Chest diagnostic CT (if pulmonary symptoms are present)**
- **Genetic counseling if patient is high risk for hereditary breast cancer[f]**
- **FDG PET/CT scan[g,h] (category 2B)**

Preoperative chemotherapy,[i] anthracycline + taxane (preferred).[i] If tumor HER2 positive, HER2-targeted therapy[j]

Response

No response

[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. The differential diagnosis includes cellulitis of the breast or mastitis. Pathologically, a tumor is typically present in the dermal lymphatics of the involved skin, but dermal lymphatic involvement is neither required, nor sufficient by itself for a diagnosis of inflammatory breast cancer.

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

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

[d]See Fertility and Birth Control (BINV-C).

[e]If FDG PET/CT is performed and clearly indicates bone metastasis on both the PET and CT component, bone scan or sodium fluoride PET/CT may not be needed.

[f]See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.

[g]FDG PET/CT can be performed at the same time as diagnostic CT. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.

[h]FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.

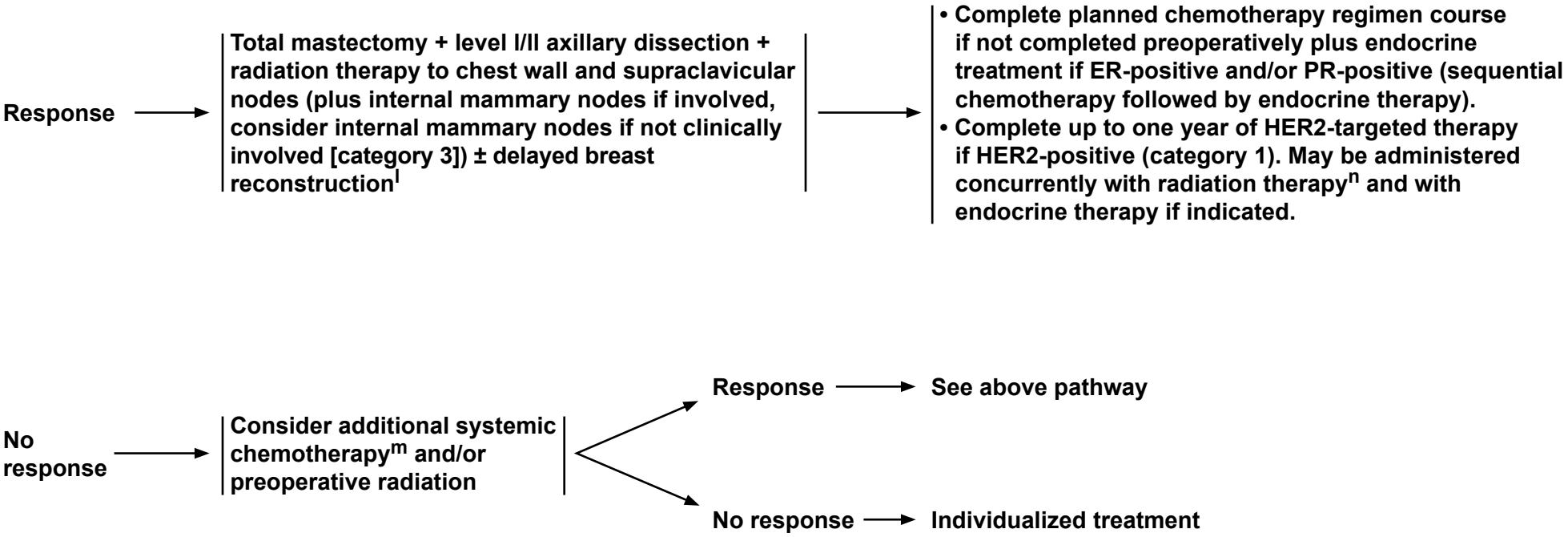
[i]See Neoadjuvant/Adjuvant Chemotherapy (BINV-K).

[j]A pertuzumab-containing regimen may be administered preoperatively to patients with HER2-positive IBC.

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TREATMENT[k]



[k]Patients with stage IV or recurrent IBC should be treated according to the guideline for recurrence/stage IV disease (BINV-17 to BINV-22).
[l]See Principles of Breast Reconstruction Following Surgery (BINV-H).
[m]See Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-N).
[n]See Principles of Radiation Therapy (BINV-I).

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Table 1

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

Primary Tumor (T) The T classification of the primary tumor is the same regardless of whether it is based on clinical or pathologic criteria, or both. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cutoff for a given T classification, it is recommended that the size be rounded to the millimeter reading that is closest to the cutoff. For example, a reported size of 1.1 mm is reported as 1 mm, or a size of 2.01 cm is reported as 2.0 cm. Designation should be made with the subscript "c" or "p" modifier to indicate whether the T classification was determined by clinical (physical examination or radiologic) or pathologic measurements, respectively. In general, pathologic determination should take precedence over clinical determination of T size.

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 NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted
T1	Tumor ≤20 mm or less in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules).

Note: Invasion of the dermis alone does not qualify as T4

T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

Staging continued on next page (ST-2)

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Table 1 (continued)

Regional Lymph Nodes (N)

Clinical

NX		Regional lymph nodes cannot be assessed (e.g., previously removed)
N0		No regional lymph node metastasis
N1		Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2		Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastases
	N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
	N2b	Metastases only in clinically detected* ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases
N3		Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases 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)

**Note: Clinically detected* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration.

Pathologic (pN)*

pNX	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis histologically

Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.

pN0(i-)	No regional lymph node metastasis histologically, negative IHC
pN0(I+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
pN0(mol-)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
pN0(mol+)	Positive molecular findings (RT-PCR),** but no regional lymph node metastases detected by histology or IHC

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

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

Staging continued on next page (ST-3)

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Table 1 (continued)

Pathologic (pN) *(continued)*

pN1 Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected***

- pN1mi Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
- pN1a Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
- pN1b Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
- pN1c Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected

pN2 Metastases in 4–9 axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases

- pN2a Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
- pN2b Metastases in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases

pN3 Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected*** ; or in ipsilateral supraclavicular lymph nodes

- pN3a Metastases in ten or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
- pN3b Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
- pN3c Metastasis in ipsilateral supraclavicular lymph nodes

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

**** "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

Distant Metastasis (M)

M0 No clinical or radiographic evidence of distant metastases

cM0(I+) No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases

M1 Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Staging continued on next page (ST-4)

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Table 1 (continued)

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0	**Stage IIIA**	T0	N2	M0
Stage IA	T1*	N0	M0		T1*	N2	M0
Stage IB	T0	N1mi	M0		T2	N2	M0
	T1*	N1mi	M0		T3	N1	M0
Stage IIA	T0	N1**	M0		T3	N2	M0
	T1*	N1**	M0	**Stage IIIB**	T4	N0	M0
	T2	N0	M0		T4	N1	M0
Stage IIB	T2	N1	M0		T4	N2	M0
	T3	N0	M0	**Stage IIIC**	Any T	N3	M0
				Stage IV	Any T	Any N	M1

* T1 includes T1mi
** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.
- M0 includes M0(i+).
- The designation pM0 is not valid; any M0 should be clinical.
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
- Stage designation may be changed if postsurgical 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.
- Postneoadjuvant therapy is designated with “yc” or “yp” prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

HISTOLOGIC GRADE (G)

All invasive breast carcinomas 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 designated as grade 1; a combined score of 6–7 points is grade 2; a combined score of 8–9 points is grade 3.

HISTOLOGIC GRADE (NOTTINGHAM COMBINED HISTOLOGIC GRADE IS RECOMMENDED)

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

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

[1]Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol 2007;25:5287–312.

[2]Singletary SE, Allred C, Ashley P, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol 2002;20:3628–36.

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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Overview

The American Cancer Society estimates that 234,190 Americans will be diagnosed with invasive breast cancer and 40,730 will die of the disease in the United States in 2015.[1] Breast cancer is the most frequently diagnosed cancer globally and is the leading cause of cancer-related death in women.[2]

The lifetime risk for breast cancer for women in the United States has increased from 1 in 11 in the 1970s to 1 in 8 today, a change related to shifting breast cancer risk factor demographics and the increased use of screening mammography. Breast cancer incidence peaked around 2000 then decreased to current rates with some variation among racial and socioeconomic groups. Between 2006 and 2010, breast cancer incidence increased slightly among African American women, decreased among Hispanic women, and was stable among whites, Asian Americans/Pacific Islanders, and American Indians/Alaska Natives. Historically, white women have had the highest breast cancer incidence rates among women aged 40 years and older; however, incidence rates are converging among white and African American women, particularly among women aged 50 years to 59 years.[3] Since 1991, breast cancer mortality has been declining[1,4] suggesting a benefit from the combination of early detection and more effective treatment.[5]

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; increased mammographic breast density; 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 Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian. Women at increased risk for breast cancer (generally those with ≥1.7% 5-year risk for breast cancer using the Gail model of risk assessment[6]) may consider risk reduction strategies (see NCCN Guidelines for Breast Cancer Risk Reduction).

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.[7] Approximately 85% to 90% of invasive carcinomas are ductal in origin.[8] The invasive ductal carcinomas include unusual variants of breast cancer, such as mucinous, adenoid cystic, and tubular carcinomas, which have especially favorable natural histories.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Breast Cancer, an electronic search of the PubMed database was performed to obtain key literature in Breast Cancer, published between 06/19/13 and 06/19/14, using the following search terms: Breast Cancer OR DCIS OR Inflammatory Breast Cancer OR Phyllodes. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[9]

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The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 592 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the Guidelines update meeting as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

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, estrogen receptor [ER], progesterone receptor [PR], human epidermal growth factor receptor 2 [HER2]). These factors are determined by examination of excised tissue and are 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, radiation therapy). The specimens should be oriented for the pathologist, and specific requests for determination of biomarkers should be stated (eg, ER, 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.[10,11] Significant omissions include failure to orient and report surgical margins and failure to report tumor grade consistently.

The College of American Pathologists (CAP) has developed pathology reporting protocols to promote complete and standardized reporting of malignant specimens. CAP provides a protocol for each disease site that includes cancer case summaries (checklists) along with background documentation. These checklists form the basis for a synoptic, standardized reporting of pathologic findings. The checklists are available without charge through the CAP website at www.cap.org. Consistent, unambiguous, and complete pathology reporting is a cornerstone of quality breast cancer care, and the NCCN Breast Cancer Panel endorses the use of the CAP protocols for reporting the pathologic analysis of all breast cancer specimens.

ER status should be determined for all samples of ductal carcinoma in situ (DCIS), and ER and PR tumor status should be determined for all samples of invasive breast cancer. ER and PR tumor status is normally determined by immunohistochemistry (IHC) testing. Although this method is considered reliable when performed by experienced pathology personnel, there have been several reports indicating that the reliability of ER and PR determinations can vary widely from one laboratory to another.[12-14] These inter-laboratory differences may be attributable to the diverse methodologies and diverse interpretation schema used to evaluate tumor hormonal status. An NCCN Task Force

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and a panel of ASCO and CAP members have reviewed this topic and issued recommendations on ER and PR testing in breast cancer.[15,16] Breast cancers that have at least 1% of cells staining positive for ER should be considered ER-positive.[15-17]

Principles of HER2 Testing

Along with ER and PR, the determination of HER2 tumor status is recommended for all newly diagnosed invasive breast cancers and for first recurrences of breast cancer whenever possible. The NCCN Breast Cancer Panel endorses CAP accreditation for anatomic pathology laboratories performing HER2 testing.

HER2 status can be assessed by measuring the number of *HER2* gene copies using in situ hybridization (ISH) techniques, or by a complementary method in which the quantity of HER2 cell surface receptors is assessed by IHC.[18] Assignment of HER2 status based on mRNA assays or multigene arrays is not recommended. The accuracy of HER2 assays used in clinical practice is a major concern, and results from several studies have shown that false-positive[19-22] as well as false-negative[19,23] HER2 test results are common. A joint panel from ASCO and CAP has issued updated HER2 testing guidelines to avoid such false-positive or false-negative results. These updated guidelines have been published in the *Archives of Pathology & Laboratory Medicine* and ASCO's *Journal of Clinical Oncology*.[24,25] The NCCN Panel endorses these updated ASCO/CAP recommendations for quality HER2 testing and has outlined these recommendations in *Principles of HER2 Testing*.

HER2 testing should be performed in laboratories accredited by CAP or another equivalent authority 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 should also include information on site of tumor, specimen type, histologic type, fixation method and time, block examined, and details on the HER2 testing method(s) used. Clinicians should be familiar with the significance of these criteria when making clinical recommendations for an individual patient.

HER2-Positive Result

Consistent with the ASCO/CAP guidelines, the NCCN Panel considers either IHC or ISH with either a single or dual probe as an acceptable method for making an initial determination of HER2 tumor status. Breast cancer tumors are classified as HER2-positive if they are scored as 3+ by an IHC method defined as uniform membrane staining for HER2 in 10% or more of tumor cells or demonstrate *HER2* gene amplification by an ISH method (single probe, average *HER2* copy number ≥6.0 signals/cell; dual probe *HER2/CEP17* ratio ≥2.0 with an average HER2 copy number ≥4.0 signals/cell; dual probe *HER2/* chromosome enumeration probe (C*EP)17* ratio ≥2.0 with an average *HER2* copy number <4.0 signals/cell; *HER2/CEP17* ratio <2.0 with an average *HER2* copy number ≥6.0 signals/cell).

High average copy number of HER2 (≥6.0 signals/cell) is considered positive regardless of the *HER2/CEP17* ratio. The rationale cited by the joint committee for including rare scenarios such as HER2 positivity when dual probe *HER2/CEP17* ratio is greater than or equal to 2.0 and average HER2 copy number is less than 4.0 signals/cell is that the first-generation trials of adjuvant trastuzumab included a small number of patients with a *HER2*/CEP17 ratio greater than or equal to 2.0 and an average *HER2* copy number less than 4.0 signals/cell. There is no trend in these data, suggesting that these patients were not

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responsive to trastuzumab and the trastuzumab has a favorable safety profile.

Equivocal Result

The NCCN Panel agrees with the ASCO/CAP HER2 committee that results of IHC are equivocal if scored as IHC 2+ "based on circumferential membrane staining that is incomplete and/or weak/moderate and within greater than 10% of the invasive tumor cells or complete and circumferential membrane staining that is intense and within less than or equal to 10% of the invasive tumor cells." In such cases, the panel recommends reflex testing using the ISH method on the same specimen *or* repeating tests if a new specimen is available.

Similarly, samples with equivocal results by an ISH assay (for example, single probe ISH average *HER2* copy number ≥4.0 and <6.0 signals/cell; and dual probe *HER/CEP17* ratio <2.0 with an average *HER2* copy number ≥4.0 signals/cell) must be confirmed by reflex testing using the IHC method on the same specimen *or* repeating tests if a new specimen is available.

Staging

All patients with breast cancer should be assigned a clinical stage of disease, and, if appropriate evaluation is available, a pathologic stage of disease. The routine use of staging allows for efficient identification of local treatment options, assists in identifying systemic treatment options, allows for the comparison of outcome results across institutions and clinical trials, and provides baseline prognostic information. Effective January 2010, the AJCC implemented a revision of the 7th edition of the AJCC Cancer Staging Manual containing important changes and additions to the TNM staging system for breast cancer.[26] This revision differs from the 2003 edition of the AJCC staging manual by providing more direction relating to the specific methods of clinical and pathologic tumor measurement; recommending that all invasive cancers should be assigned a combined histologic tumor grade using the Elston-Ellis modification of the Scarff-Bloom-Richardson grading system; providing clarification of the classification of isolated tumor cells in axillary lymph node (ALN) staging; subdividing stage I into stage IA and IB based upon the presence or absence of nodal micrometastases (N0 versus N0mi+); and defining a new category of M0(i+) disease referring to tumor cells microscopically detectable in bone marrow or circulating blood or found incidentally in other tissues not exceeding 0.2 mm in patients who have no signs or symptoms of metastasis. This version of the AJCC staging manual also recommends the collection of biomarkers such as hormone receptor status (ER and PR) and HER2 status, although these characteristics do not specifically influence assigned stage of disease.

Treatment Approach

The treatment of breast cancer includes the treatment of local disease with surgery, radiation therapy, or both, and systemic treatment with chemotherapy, endocrine therapy, biologic therapy, or combinations of these. The need for and selection of various local or systemic therapies are based on several prognostic and predictive factors. These factors include tumor histology, clinical and pathologic characteristics of the primary tumor, ALN status, tumor hormone receptor (ER/PR) content, tumor HER2 status, multi-gene testing, presence or absence of detectable metastatic disease, patient comorbid conditions, patient age, and menopausal status. One-percent of breast cancers occur in men,[1] 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.[27,28] Patient preference is a major component of the

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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 DCIS (stage 0); 2) operable, locoregional invasive carcinoma with or without associated noninvasive carcinoma (clinical stage I, stage II, and some stage IIIA tumors); 3) inoperable locoregional invasive carcinoma with or without associated noninvasive carcinoma (clinical stage IIIB, stage IIIC, and some stage IIIA tumors); and 4) metastatic (stage IV) or recurrent carcinoma.

Pure Noninvasive Carcinomas (Stage 0)

Both LCIS and DCIS may be difficult to distinguish from atypical hyperplasia or from invasive carcinomas with early invasion.[29,30] 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. Genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer as defined by the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian. 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 with invasive disease, even if microinvasive, on pathology review or during re-excision, mastectomy, or ALN staging should be treated according to the stage-appropriate guideline for invasive carcinoma.

Lobular Carcinoma in Situ
(Stage 0, Tis, N0, M0)

Workup

Recommended workup includes history and physical examination, diagnostic bilateral mammography, and pathology review.

Primary Treatment

Controversy exists regarding whether an open surgical excision should be performed of the region of LCIS diagnosed by core biopsy and that is not associated with a mammographic structural abnormality or residual mammographic calcifications. Small retrospective studies have concluded that excision following the diagnosis of LCIS on core needle biopsy is not necessary.[31-33] Other studies have shown that 17% to 27% of patients with LCIS diagnosed by core needle biopsy are upgraded to having invasive cancer or DCIS after larger excisional biopsy.[34-38] Based on core needle biopsies, it may be possible to identify subsets of patients with LCIS who can be safely spared a surgical excision.[33] There are some data of small groups of patients suggesting that LCIS subtypes, including pleomorphic LCIS and LCIS associated with necrosis, carry a risk for associated invasive carcinoma similar to DCIS. Therefore, according to the NCCN Panel, it is reasonable to perform surgical excision of LCIS found in a core biopsy to exclude an associated invasive cancer or DCIS. More than 4 foci of LCIS may also increase the risk for upstaging on surgical biopsy.[39] The NCCN Panel recommends that LCIS of the usual type (involving <4 terminal ductal lobular units in a single core) found on core biopsy, as a result of routine screening for calcifications and without imaging discordance, may be managed by imaging follow-up.

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.[40] Clinicians may consider complete excision with negative margins for

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pleomorphic LCIS. 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.

Patients with a confirmed diagnosis of LCIS should be counseled regarding reducing the risk of developing invasive cancer (see NCCN Guidelines for Breast Cancer Risk Reduction).

Surveillance

Follow-up of patients with LCIS includes interval history and physical examinations every 6 to 12 months. Annual diagnostic mammography is recommended in patients being followed with clinical observation; see also the NCCN Guidelines for Breast Cancer Screening and Diagnosis. Patients receiving a risk reduction agent should be monitored as described in the NCCN Guidelines for Breast Cancer Risk Reduction.

Ductal Carcinoma in Situ

(Stage 0, Tis, N0, M0)

Workup

The recommended workup and staging of DCIS includes: history and physical examination; bilateral diagnostic mammography; pathology review; and tumor ER determination. Genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer as defined by the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.

Although HER2 status is of prognostic significance in invasive cancer, its importance in DCIS has not been elucidated. To date, studies have either found unclear or weak evidence of HER2 status as a prognostic indicator in DCIS.[41-44] The NCCN Panel concluded that knowing the HER2 status of DCIS does not alter the management strategy and routinely should not be determined.

MRI has been prospectively shown to have a sensitivity of up to 98% for high-grade DCIS.[45] In a prospective, observational study, 193 women with pure DCIS underwent both mammography and MRI imaging preoperatively; 93 (56%) women were diagnosed by mammography and 153 (92%) were diagnosed by MRI ($P < .0001$). Of the 89 women with high-grade DCIS, 43 (48%) who were not diagnosed by mammography were diagnosed by MRI alone. Another study evaluated the role of MRI in determining appropriate candidacy for partial breast irradiation for women with DCIS. Twenty percent of women with DCIS were identified as ineligible for partial breast irradiation after a bilateral breast MRI.[46] However, large prospective clinical trials will be necessary to further investigate the clinical role of MRI for diagnosing DCIS and to investigate its effect on recurrence rates or mortality. The NCCN Panel has included breast MRI as optional during the initial workup of DCIS, noting that the use of MRI has not been shown to increase likelihood of negative margins or decrease conversion to mastectomy with DCIS.

Primary Treatment

Seemingly pure DCIS on core needle biopsy will be found to be associated with an invasive cancer on surgical excision in about 25% of patients.[47]

For the vast majority of patients with limited disease where negative margins are achieved with the initial excision or with re-excision, lumpectomy 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.[48-50]

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Patients with DCIS and evidence of widespread disease (ie, disease in two or more quadrants) on mammography or other imaging, physical examination, or biopsy require a total mastectomy without lymph node dissection.

Many factors impact recurrence risk, including patient age, tumor size, tumor grade, and margin width. 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 accepted as negative (but may be excessive and may compromise cosmetic outcome) and margins less than 1 mm are inadequate, but no uniform consensus exists for margin status between these values. With pathologic margins between 1 and 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.

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 survival[48,49,51-55] or distant metastasis-free survival.[56] Whole breast irradiation after breast-conserving surgery reduces the relative risk of a local failure by approximately one half. If whole breast radiation is used, 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.[57-60] For example, in a retrospective review, 10-year disease-free survival (DFS) rates of 186 patients with DCIS treated with lumpectomy alone were 94% for patients with low-risk DCIS and 83% for patients with both intermediate- and high-risk DCIS.[57]

In another retrospective study of 215 patients with DCIS treated with lumpectomy 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.[58]

A multi-institutional, nonrandomized, prospective study of selected patients with low-risk DCIS treated without radiation has also provided some support for the use of excision without radiation in the treatment of DCIS.[61] At a median follow-up of 6.2 years, the 5-year risk of ipsilateral breast recurrence was 6.1% (95% confidence interval [CI], 4.1%–8.2%) in the subset of patients with low-/intermediate-grade DCIS and median tumor size of 6 mm. Margin widths were greater than or equal to 5 mm in 69.2% and 82.9% of patients in the low-/intermediate-risk and high-risk arms, respectively, with margin widths of greater than or equal to 10 mm or no tumor on re-excision observed in 48.5% and 53.3% of patients in the respective groups.[61] Although an acceptably low ipsilateral recurrence rate was observed in the low-/intermediate-grade arm of the study at 5 years, the 7-year ipsilateral recurrence rate in this group of patients was considerably higher (10.5%; 95% CI, 7.5%–13.6%), suggesting that these events may be delayed but not prevented in this population. Ipsilateral breast recurrences were approximately equally divided between invasive breast cancer and DCIS in the low-/intermediate-risk group but only about one-third of patients with an in-breast recurrence in the high-risk group had invasive disease.

Another retrospective study reviewed 220 patients with DCIS treated with breast conservation surgery and radiation. Thirty-six percent

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received a radiation boost. At 46 months, none of the 79 patients who received a radiation boost experienced a local recurrence, whereas 8 of 141 patients who did not receive a boost experienced a local recurrence.[62]

Prospective randomized trials have not been carried out to analyze whether wider margins can replace the need for radiation therapy for DCIS. A retrospective series demonstrated that for margin width of 10 mm, radiation had no additional benefit in reducing the already low local recurrence rate of 4% at the end of 8 years.[60] Also, if margin width was between 1 mm and less than 10 mm, the addition of radiation therapy led to a non-statistically significant reduction in local recurrence. However, when margins were less than 1 mm a significant benefit was seen.[60]

A meta-analysis of four large multicentre randomized trials confirmed the results of the individual trials that adding radiation therapy to breast-conserving surgery for DCIS provides a statistically and clinically significant reduction in ipsilateral breast events (HR [hazard ratio], 0.49; 95% CI; 0.41–0.58, $P < .0000$).[63]

Results from a retrospective study of 445 patients with pure DCIS treated by excision alone indicated that margin width was the most important independent predictor of local recurrence, although the trend for decreasing local recurrence risk with increasing margin width was most apparent with margins less than 1 mm and greater than or equal to 10 mm.[64]

In a meta-analysis of 4660 patients with DCIS treated with breast-conserving surgery and radiation, a surgical margin of less than 2 mm was associated with increased rates of ipsilateral breast tumor recurrence compared with margins of 2 mm, although no significant differences were observed when margins of greater than 2 mm to 5 mm or greater than 5 mm were compared with 2-mm margins.[65] The results of this study suggest that wide margins (≥2 mm), which can compromise cosmetic outcome, do not provide additional benefit in the population of patients with DCIS receiving radiation therapy following breast-conserving therapy. A large, retrospective study found that narrow surgical resection margin (≤2 mm) does not increase local recurrence compared to a surgical resection margin of 2 mm.[66] 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.

The choice of local treatment does not impact overall disease-related survival; therefore, the individual patient's acceptance of the potential for an increased risk of local recurrence must be considered.

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).[67]

Axillary dissection is not recommended for patients with pure DCIS, and axillary nodal involvement in patients with pure DCIS in the breast is rare.[68] However, a small proportion of women with seemingly pure DCIS on initial biopsy will have invasive breast cancer at the time of the definitive surgical procedure and thus will ultimately require ALN staging. In patients with seemingly 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 (SLN) procedure, an SLN procedure may be considered.[69-71]

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NCCN Recommendations for Primary Treatment of DCIS

According to the NCCN Panel, primary treatment options for women with DCIS along with their respective categories of consensus are: lumpectomy plus radiation (category 1); total mastectomy, with or without reconstruction (category 2A); or 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).

According to the NCCN Panel, 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. Clips are used to demarcate the biopsy area because DCIS may be clinically occult and further surgery may be required pending the margin status review by pathology.

Women treated with mastectomy are appropriate candidates for breast reconstruction (see *Principles of Breast Reconstruction Following Surgery* in the NCCN Guidelines for Breast Cancer). Contraindications to breast-conserving therapy with radiation therapy are listed in the algorithm (see *Special Considerations to Breast-Conserving Therapy Requiring Radiation Therapy* in the NCCN Guidelines for Breast Cancer).

Postsurgical Treatment

DCIS falls between atypical ductal hyperplasia and invasive ductal carcinoma within the spectrum of breast proliferative abnormalities. The Breast Cancer Prevention Trial performed by National Surgical Adjuvant Breast and Bowel Project (NSABP) showed a 75% reduction in the occurrence of invasive breast cancer in patients with atypical ductal hyperplasia treated with tamoxifen.[72,73] These data also showed that tamoxifen led to a substantial reduction in the risk of developing benign breast disease.[74] The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 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.[4]

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. With 13.6 years median follow-up, the women treated with tamoxifen had a 3.4% absolute reduction in ipsilateral in-breast tumor recurrence risk (HR, 0.30; 95% CI, 0.21–0.42; $P < .001$) and a 3.2% absolute reduction in contralateral breast cancers (HR, 0.68; 95% CI, 0.48–0.95; $P = .023$).[55] The women receiving tamoxifen had a 10-year cumulative rate of 4.6% for invasive and 5.6% for noninvasive breast cancers in the ipsilateral breast compared with 7.3% for invasive and 7.2% for noninvasive breast cancers in placebo-treated women. The cumulative 10-year frequency of invasive and noninvasive breast cancer in the contralateral breast was 6.9% and 4.7% in the placebo and tamoxifen groups, respectively. No differences in overall survival (OS) were noted. A retrospective analysis of ER expression in NSABP B-24 suggests that increased levels of ER expression predict for tamoxifen benefit in terms of risk reduction for ipsilateral and

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contralateral breast cancer development following breast-conserving therapy.[75]

A phase III trial for women with excised DCIS randomized subjects in a 2 x 2 fashion to tamoxifen or not and whole breast radiation therapy or not.[54] With 12.7 years of median follow-up, the use of tamoxifen decreased all new breast events (HR, 0.71; 95% CI, 0.58–0.88; *P* = .002). The use of tamoxifen decreased ipsilateral and contralateral breast events in the subjects not given whole breast radiotherapy (ipsilateral HR, 0.77; 95% CI, 0.59–0.98; contralateral HR, 0.27; 95% CI 0.12–0.59), but not in those receiving whole breast radiotherapy (ipsilateral HR, 0.93; 95% CI, 0.50–1.75; *P* = .8; contralateral HR, 0.99; 95% CI, 0.39–2.49; *P* = 1.0).

NCCN Recommendations

According to the NCCN Panel, tamoxifen may be considered as a strategy to reduce the risk of ipsilateral breast cancer recurrence in women with ER-positive DCIS treated with breast-conserving therapy (category 1 for those undergoing breast-conserving surgery followed by radiation therapy; category 2A for those undergoing excision alone). The benefit of tamoxifen for ER-negative DCIS is not known.

Strategies for reducing the risk of recurrence to the contralateral breast are described in the NCCN Guidelines for Breast Cancer Risk Reduction.

Surveillance

According to the NCCN Panel, follow-up of women with DCIS includes interval history and physical examination every 6 to 12 months for 5 years and then annually, as well as yearly diagnostic mammography. In patients treated with breast-conserving therapy, the first follow-up mammogram should be performed 6 to 12 months after the completion of breast-conserving radiation therapy (category 2B). Patients receiving risk reduction agents should be monitored as described in the NCCN Guidelines for Breast Cancer Risk Reduction.

The majority of recurrences of DCIS are in-breast recurrences after breast-conserving therapy, and recurrences mostly occur close to the site of prior disease. In those women for whom the initial DCIS was treated with excision alone, the treatment for a recurrence of DCIS is similar to that followed previously. In women whom the initial DCIS was treated with breast-conserving surgery plus radiation therapy, mastectomy is usually necessary to treat DCIS recurrence. Local recurrences after mastectomy for DCIS should be treated with wide local excision with consideration for chest wall irradiation.

Overall, approximately half of the local recurrences after 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.

Invasive Breast Cancer

Stage I, IIA, IIB, or T3, N1, M0

Workup

The recommended workup of localized invasive breast cancer includes: history and physical exam; a complete blood count (CBC); liver function tests**;** bilateral diagnostic mammography; breast ultrasonography, if necessary; tumor ER and PR determinations; HER2 tumor status determination; and pathology review.

Use of MRI is optional and is not universally recommended by experts in the field. Breast MRI advocates note its high sensitivity for evaluation of extent of disease, particularly for invasive cancer and in dense

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breasts where mammographically occult disease is more likely to elude preoperative detection. MRI detractors note that MRI has a high percentage of false-positive findings requiring diagnostic workup in many circumstances including MRI-guided biopsy.[76-78] Patients should not be denied the option of breast conservation therapy based on MRI findings alone without additional tissue sampling to verify that these findings represent true malignant disease warranting excision. There also are suggestions that MRI use may increase mastectomy rates by identifying mammographically occult disease satellites that would have been adequately treated with post-lumpectomy radiation had the disease remained undiscovered without assessing extent of disease using MRI.[79]

Two prospective randomized studies assessing the utility of MRI for determining extent of disease prior to surgical resection have been performed, and neither showed improvement in post-lumpectomy re-excision rates.[80,81] One retrospective study suggested an outcome benefit[82] whereas another did not.[83] One systematic review[78] documented breast MRI staging to alter surgical treatment in 7.8% to 33.3% of women.[78] However, no differences in outcome, if any, have yet been demonstrated.

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. A specific indication for MRI imaging of the breast is in patients presenting with cancer in the axillary nodes without a known breast primary. In these cases, patients in whom the mammographically occult breast primary is found will be able to forego mastectomy and instead have breast conservation therapy. MRI also may be useful for breast cancer evaluation before and after neoadjuvant therapy to define the extent of disease, response to treatment, and potential for breast-conserving therapy.

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, ER, PR, HER2). These factors are determined by examination of excised tissue and are 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, radiation therapy). The specimens should be oriented for the pathologist, and specific requests for determination of biomarkers should be stated (eg, ER, PR, and HER2 status). 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.[10,11] Significant omissions include failure to orient and report surgical margins and failure to report tumor grade consistently. CAP has developed pathology reporting protocols to promote complete and standardized reporting of malignant specimens (www.cap.org). The NCCN Breast Cancer Panel endorses the use of the CAP protocols for reporting the pathologic analysis of all breast cancer specimens.

Genetic counseling: For patients considered to be at high risk for hereditary breast cancer as defined by the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, genetic counseling is recommended

Distress Assessment: Factors impacted by cancer treatments such as body image among many others contribute to psychosocial distress. Younger women have higher rates of psychosocial distress than women diagnosed at older ages.[84-88] The levels of distress vary from patient to patient and need to be addressed individually. The NCCN Breast Cancer Panel recommends accessing for distress in patients newly diagnosed with breast cancer.

Fertility Counseling: Numerous epidemiologic studies have demonstrated that child-bearing after treatment for invasive breast cancer does not increase rates of recurrence or death from breast cancer. [89] The offspring of pregnancies after treatment for breast cancer do not have an increased rate of birth defects or other serious childhood illness. However, treatment for breast cancer, especially with cytotoxic agents, may impair fertility. Therefore, it is reasonable and appropriate to consider fertility preservation prior to breast cancer treatment in young women who desire to bear children following breast cancer therapy.[90-94] No high-level evidence demonstrates that ovarian suppression or other interventions decrease the toxicity of cytotoxic chemotherapy on the premenopausal ovary.[95] However, many women, especially those younger than age 35, regain menstrual function within 2 years of completing chemotherapy.[96] Resumption of menses does not necessarily correlate with fertility, and fertility may be preserved without menses.

All premenopausal patients should be informed about the potential impact of chemotherapy on fertility and asked about their desire for potential future pregnancies. Should a newly diagnosed premenopausal woman with breast cancer desire to bear children after breast cancer treatment, she should receive consultation with a physician with expertise in fertility prior to the initiation of chemotherapy.[94,97] Multiple factors to consider in making a decision for fertility preservation include patient preference, the age of the woman, risk of premature ovarian failure based on anticipated chemotherapy, and length of optimal endocrine therapy. It is important for fetal safety that women do not become pregnant during breast cancer treatment. Also see NCCN Guidelines for Adolescent and Young Adult Oncology.

Additional Workup Directed by Signs and Symptoms

The panel has re-iterated that routine systemic imaging is ***not*** indicated for patients with early breast cancer *in the absence* of signs/symptoms of metastatic disease.[98] These recommendations are supported by a study evaluating patients with newly diagnosed breast cancer by bone scan, liver ultrasonography, and chest radiography.[99] 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.[99]

Additional tests may be considered only based on the signs and symptoms. A chest diagnostic CT is indicated only if pulmonary symptoms are present. Likewise, abdominal imaging using diagnostic CT or MRI is indicated only if the patient has elevated alkaline phosphatase, abnormal results on liver function tests, abdominal symptoms, or abnormal physical examination of the abdomen or pelvis.

A bone scan is *only* indicated in patients presenting with localized bone pain or elevated alkaline phosphatase. The use of PET or PET/CT scanning is *not indicated* in the staging of clinical stage I, II, or operable III breast cancer. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease. The NCCN Panel recommends *against* the use of PET or PET/CT scanning in the staging

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of these early-stage patients. The recommendation against the use of PET scanning is supported by the high false-negative rate in the detection of lesions that are small (<1 cm) and/or low grade, the low sensitivity for detection of axillary nodal metastases, the low prior probability of these patients having detectable metastatic disease, and the high rate of false-positive scans.[100-103]

Locoregional Treatment

Surgery

Several randomized trials document that mastectomy is equivalent to breast-conserving therapy (lumpectomy with whole breast irradiation) as primary breast local treatment for the majority of women with stage I and stage II breast cancers (category 1).[104-108]

After surgical resection, a careful histologic assessment of resection margins is essential. The NCCN Panel notes that usefulness of lumpectomy is predicated on achieving pathologically negative margins after resection. The NCCN Panel accepts the most recent definition outlined in the guidelines established by the Society of Surgical Oncology (SSO)/American Society for Radiation Oncology (ASTRO) of no ink on a tumor as the standard for negative surgical margins for invasive cancer (with or without a component of DCIS).[109] For pure DCIS, the definition of negative margins remains a topic of discussion and debate.

If margins remain positive after further surgical re-excision(s), then mastectomy may be required for optimal local disease control. In order to adequately assess margins following lumpectomy, the panel recommends that the surgical specimens be directionally oriented and that the pathologist provide descriptions of the gross and microscopic margin status and the distance, orientation, and type of tumor (invasive cancer or pure DCIS) in relation to the closest margin. Marking the tumor bed with clips facilitates accurate planning of the radiation boost field, where appropriate. It may be reasonable to treat selected patients with invasive cancer (without extensive intraductal component) despite a microscopically focally positive margin with breast conservation therapy. For these patients, the utilization of a radiation boost after whole breast radiation should be considered. While standard doses of radiation boost from the randomized clinical trials range from 10 to 16 Gy, the higher doses in this spectrum are often reserved for patients perceived to be at higher risk for local recurrence (age <50, high grade or focally positive margins).

Lumpectomy is contraindicated for patients who 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.

Relative contraindications to lumpectomy include previous radiation therapy to the breast or chest wall; active connective tissue disease involving the skin (especially scleroderma and lupus), tumors greater than 5 cm (category 2B), and diffusely positive pathologic margins.

Several studies of women with early-stage breast cancer treated with lumpectomy have identified young age as a significant predictor of an increased likelihood of ipsilateral breast tumor recurrences after lumpectomy.[110-112] Risk factors, such as a family history of breast cancer or a genetic predisposition for breast cancer (eg, *BRCA1/2* or other cancer predisposing 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.[113]

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Survival outcomes for young women with breast cancer receiving either lumpectomy or mastectomy are similar.[114]

Only limited data are available on the survival impact of mastectomy contralateral to a unilateral breast cancer.[115] Analysis of women included in the SEER database treated with mastectomy for a unilateral breast cancer from 1998 to 2003 showed that contralateral prophylactic mastectomy (CPM) performed at the time of treatment of a unilateral cancer was associated with a reduction in breast cancer-specific mortality only in the population of young women (18–49 years of age) with stage I/II, ER-negative breast cancer (HR, 0.68; 95% CI, 0.53–0.88; *P* = .004).[116] The 5-year breast cancer survival for this group was *slightly* improved with contralateral mastectomy versus without (88.5% vs. 83.7%, difference = 4.8%).[116] These differences observed in retrospective analysis could be due to selection bias among patients who chose CPM.[117] A statistical simulation of survival outcomes after CPM and no CPM among women with stage I or II breast cancer without a *BRCA* mutation found that the absolute 20-year survival benefit from CPM was less than 1% among all age, ER status, and cancer stage groups.[118] Data from a recent meta-analysis found no absolute reduction in risk of distant metastases with CPM.[119] Furthermore, among patients with unilateral breast cancer who have an increased familial/genetic risk, although a decrease in metastatic contralateral breast cancer incidence was observed in those who received CPM, no improvement was seen in OS of these patients.[119]

The panel recommends that women with breast cancer who are less than or equal to 35 years or premenopausal and carriers of a known *BRCA1/2* mutation consider additional risk reduction strategies following appropriate risk assessment and counseling (see NCCN Guidelines for Breast Risk Reduction and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian). This process should involve multidisciplinary consultations prior to surgery, and should include a discussion of the risks associated with development of a contralateral breast cancer as compared with the risks associated with recurrent disease from the primary cancer. Except as specifically outlined in these guidelines, prophylactic mastectomy of a breast contralateral to a known unilateral breast cancer treated with mastectomy is discouraged by the panel. The use of a prophylactic mastectomy contralateral to a breast treated with lumpectomy is very strongly discouraged in all patients.

Surgical Axillary Staging

The NCCN Guidelines for Breast Cancer include a section for surgical staging of the axilla for stages I, IIA, IIB, and IIIA (T3, N1, M0) breast cancer. Pathologic confirmation of malignancy using ultrasound-guided fine-needle aspiration (FNA) or core biopsy must be considered in patients with clinically positive nodes to determine whether ALN dissection is needed.

Performance of SLN mapping and resection in the surgical staging of the clinically negative axilla is recommended by the panel for assessment of the pathologic status of the ALNs in patients with clinical stage I, stage II, and stage IIIA (T3, N1, M0) breast cancer.[71,120-128] This recommendation is supported by results of randomized clinical trials showing decreased arm and shoulder morbidity (eg, pain, lymphedema, sensory loss) in patients with breast cancer undergoing SLN biopsy compared with patients undergoing standard ALN dissection.[128,129] No significant differences in the effectiveness of the SLN 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 SLN resection. An experienced SLN team is mandatory for the use of SLN mapping and excision.[130,131] Women who have clinical stage I or II disease and do not have immediate

access to an experienced SLN team should be referred to an experienced SLN team for the definitive surgical treatment of the breast and surgical ALN staging. In addition, potential candidates for SLN mapping and excision should have clinically negative ALNs at the time of diagnosis, or a negative core or FNA biopsy of any clinically suspicious ALN(s). In many institutions, SLNs are assessed for the presence of metastases by both hematoxylin and eosin (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 does not recommend routine cytokeratin IHC to define node involvement and believes that current treatment decisions should be made based solely on H&E staining. This recommendation is further supported by a randomized clinical trial (ACOSOG Z0010) for patients with H&E negative nodes where further examination by cytokeratin IHC was not associated with improved OS over a median of 6.3 years.[132] In the uncommon situation in which H&E staining is equivocal, reliance on the results of cytokeratin IHC is appropriate. Multiple attempts have been made to identify cohorts of women with involved SLNs who have a low enough risk for non-SLN involvement that complete axillary dissection might be avoided if the SLN is positive. None of the early studies identified a low-risk group of patients with positive SLN biopsies but consistently negative non-sentinel nodes.[133-139] Nonetheless, a randomized trial (ACOSOG Z0011) compared SLN resection alone with ALN dissection in women greater than or equal to 18 years of age with T1/T2 tumors, fewer than 3 positive SLNs, and undergoing breast-conserving surgery and whole breast irradiation. In this study, there was no difference in local recurrence, DFS, or OS between the two treatment groups. Only ER-negative status, age less than50, and lack of adjuvant systemic therapy were associated with decreased OS.[140] At a median follow-up of 6.3 years, locoregional recurrences were noted in 4.1% of the ALN dissection group (n = 420) and 2.8% of the SLN dissection patients (n = 436) (*P* = .11). Median OS was approximately 92% in each group.[141] Therefore, based on these results after SLN mapping and excision, if a patient has a T1 or T2 tumor with 1 to 2 positive SLNs, did not receive neoadjuvant therapy, and is treated with lumpectomy and whole breast radiation, the panel recommends no further axillary surgery.

The panel recommends level I or II axillary dissection 1) when patients have clinically positive nodes at the time of diagnosis that is confirmed by FNA or core biopsy; or 2) when sentinel nodes are not identified. For patients with clinically negative axillae who are undergoing mastectomy and for whom radiation therapy is planned, the panel notes that axillary radiation may replace axillary dissection level I/II for regional control of disease.

Traditional level I and level II evaluation of ALN requires that at least 10 lymph nodes should be provided for pathologic evaluation to accurately stage the axilla.[142,143] ALN should be extended to include level III nodes only if gross disease is apparent in the level II nodes. In the absence of gross disease in level II nodes, lymph node dissection should include tissue inferior to the axillary vein from the latissimus dorsi muscle laterally to the medial border of the pectoralis minor muscle (level I/II).

Furthermore, according to the panel, without definitive data demonstrating superior survival with ALN dissection or SLN resection, these procedures may be considered optional in patients who have particularly favorable tumors, patients for whom the selection of adjuvant systemic therapy will not be affected by the results of the procedure, elderly patients, and patients with serious comorbid

conditions. Women who do not undergo ALN dissection or ALN irradiation are at increased risk for ipsilateral lymph node recurrence.[144]

Radiation Therapy

Whole Breast Radiation

Whole breast radiation reduces the risk of local recurrence and has shown to have a beneficial effect on survival.[105,108] 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.[145,146] The panel recommends whole breast irradiation to include the majority of the breast tissue and that breast irradiation be performed following CT-based treatment planning 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), intensity-modulated radiation therapy (IMRT),[147,148] respiratory gating, or prone positioning[149] is recommended.

Dose and fractionation: Four randomized clinical trials[150-153] have investigated hypofractionated whole breast radiation schedules (39–42.9 Gy in single fractions of 2.6–3.3 Gy) compared to standard 50 Gy in single fractions of 2 Gy. The 10-year follow-up data from the START trials[154] are consistent with the 10-year results of the Canadian trial,[153] which reported that local tumor control and breast cosmesis were similar with a regimen of 42.5 Gy in 16 fractions over 3.2 weeks compared with 50 Gy in 25 fractions over 5 weeks.[153] The START trials reported radiation-related effects to normal breast tissue such as breast shrinkage, telangiectasia, and breast edema as less common with the hypofractionated fraction regimen.[154] The NCCN Panel recommends either a dose of 45 to 50 Gy in 23 to 25 fractions or 40 to 42.5 Gy in 15 to 16 fractions for whole breast radiation. Based on convenience and the data from the START trials,[154] the short course of radiation therapy (40–42.5 Gy in 15–16 fractions) is the NCCN-preferred option.

A boost to the tumor bed is recommended by the NCCN Panel in patients at higher risk (age <50, high-grade disease, or patients with focally positive margins).[155] This can be achieved with brachytherapy or electron beam or photon fields. Typical doses are 10 to 16 Gy at 2 Gy per fraction.

Regional Nodal Irradiation

The guidelines include a recommendation for regional lymph node irradiation in patients treated with lumpectomy in situations analogous to those recommended for patients treated with post-mastectomy irradiation (see *Principles of Radiation Therapy* in the NCCN Guidelines for Breast Cancer). Support for this recommendation comes from the NCIC-CTG MA.20 trial that randomized women undergoing lumpectomy and whole breast irradiation to receive regional lymph node irradiation or not. With a median follow-up of 62 months, the addition of radiation therapy reduced locoregional recurrences (HR, 0.59; P = .02) and increased DFS (HR, 0.68; P = .003), and there was a trend towards improved OS (HR, 0.76; P = .07).[156]

Accelerated Partial Breast Irradiation

Several studies have been reported using accelerated partial breast irradiation (APBI) rather than whole breast irradiation following complete surgical excision of in-breast disease. The panel generally views the use of APBI as investigational, and encourages its use within the confines of a high-quality, prospective clinical trial.[157] For patients who are not trial eligible, recommendations from ASTRO indicate that APBI may be suitable in selected patients with early-stage breast cancer and may be comparable to treatment with standard whole-breast RT.[158] Patients who may be suitable for APBI are women 60 years of age and

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older who are not carriers of a known *BRCA1/2* mutation and who have been treated with primary surgery for a unifocal stage I, ER-positive cancer. Tumors should be infiltrating ductal or have a favorable histology, should not be associated with an extensive intraductal component or LCIS, and should have negative margins. Thirty-four Gy in 10 fractions delivered twice per day with brachytherapy or 38.5 Gy in 10 fractions delivered twice per day with external beam photon therapy to the tumor bed is recommended. Other fractionation schemes are under investigation. Studies have suggested that the ASTRO stratification guidelines may not adequately predict ipsilateral breast tumor recurrences following APBI.[159,160] Follow-up is limited and studies are ongoing.

Radiation Therapy in Patients Receiving Neoadjuvant Therapy

The panel recommends that decisions related to administration of radiation therapy for patients receiving neoadjuvant chemotherapy should be made based on pre-chemotherapy tumor characteristics, irrespective of tumor response to preoperative systemic therapy (ie, radiation therapy is recommended in patients with clinical stage III disease and a pathologic complete response (pCR) to neoadjuvant chemotherapy).

Radiation Therapy after Lumpectomy

Postoperative radiation therapy is strongly recommended after lumpectomy. This is based on the beneficial effects of radiation therapy in reducing recurrences and improving OS.[108]

If adjuvant chemotherapy is indicated after lumpectomy, radiation should be given after chemotherapy is completed.[161,162] This recommendation is based on results of the "Upfront-Outback" trial in which patients who had undergone breast-conserving surgery and axillary dissection were randomly assigned to receive chemotherapy following radiation therapy or radiation therapy following chemotherapy. The initial results showed an increased rate of local recurrence in the group with delayed radiotherapy at a median follow-up of 58 months;[162] however, differences in rates of distant or local recurrence were not statistically significant when the two arms were compared at 135-month follow-up.[161]

Results from the randomized NCIC-CTG MA.20 trial demonstrate that additional regional node irradiation reduces the risk of locoregional and distant recurrence and improves DFS.[156] The study enrolled 1832 women; most (85%) had 1 to 3 positive lymph nodes, and a smaller proportion (10%) had high-risk, node-negative breast cancer. All women had been treated with lumpectomy and adjuvant chemotherapy and/or endocrine therapy. The participants were randomized to receive either whole breast radiation therapy alone or whole breast radiation plus regional node radiation therapy. The interim data found that after a median follow-up of 62 months, there were statistically significant benefits for the group receiving the added regional node radiation therapy. These included improvement in DFS (HR, 0.68; P = .003, 5-year risk: 89.7% and 84.0%) and OS (HR, 0.76; P = .07, 5-year risk: 92.3% and 90.7%).[156] The consensus of the panel is that radiation therapy should be given to the chest wall (category1), infraclavicular, and supraclavicular areas. The panel also recommends strong consideration of ipsilateral internal mammary field radiation therapy in these patients (category 2B).

There is a demonstrated benefit favoring a boost in patients with positive axillary nodes, lymphovascular invasion, young age, or high-grade disease after lumpectomy. For example, a subset analysis from an EORTC trial found that a boost dose of 16 Gy significantly reduced local relapse rate among patients at highest risk. For patients younger than 50 years old and in patients with high-grade invasive ductal

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carcinoma, the boost dose reduced the local relapse from 19.4% to 11.4% and from 18.9% to 8.6%, respectively.[163] Hence, the panel recommends consideration of a boost to the tumor bed after lumpectomy and whole breast irradiation. Administration of whole breast irradiation therapy following lumpectomy is a category 1 recommendation for patients with node-positive disease.

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 greater than or equal to 70 years of age at diagnosis, patients were randomized to receive lumpectomy with whole breast radiation or lumpectomy alone, both with tamoxifen for five years. Locoregional recurrence rates were 1% in the lumpectomy, radiation, and tamoxifen arm and 4% in the lumpectomy plus tamoxifen arm. There were no differences in OS, DFS, or need for mastectomy.[164] These results were confirmed in an updated analysis of this study with a median follow-up of 12.6 years.[165] At 10 years, 90% of patients in the lumpectomy and tamoxifen arm compared with 98% in the lumpectomy, radiation, and tamoxifen arm were free from locoregional recurrence. [165] Similar results were obtained in another study of similar design.[166] The NCCN Guidelines allow for the use of lumpectomy (pathologically negative margin required) plus tamoxifen or an aromatase inhibitor without breast irradiation in women greater than or equal to 70 years of age with clinically negative lymph nodes and ER-positive, T1 breast cancer (category 1).

Radiation Therapy After Mastectomy

Node-Positive Disease

Three randomized clinical trials have shown that a DFS and OS advantage is conferred by the irradiation of chest wall and regional lymph nodes in women with positive ALNs after mastectomy and ALN dissection.[167-171] In these trials, the ipsilateral chest wall and the ipsilateral locoregional lymph nodes were irradiated. Based on these studies, the current guidelines recommend postmastectomy irradiation in women with 4 or more positive ALNs and strong consideration of postmastectomy irradiation in women with 1 to 3 positive ALNs. Two retrospective analyses have provided evidence for benefit of radiation therapy for only selected patients receiving preoperative systemic therapy prior to mastectomy.[172,173]

Women with 4 or more positive ALNs are at substantially increased risk for locoregional recurrence of disease. The use of prophylactic chest wall irradiation in this setting substantially reduces the risk of local recurrence.[105] The use of postmastectomy, post-chemotherapy chest wall irradiation, and regional lymph node irradiation is recommended (category 1).

The recommendation for strong consideration of chest wall and supraclavicular irradiation in women with 1 to 3 involved ALNs 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 Cooperative Group.[174] In this analysis, a substantial survival benefit was associated with postmastectomy radiation therapy for women with 1 to 3 positive ALNs. 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, since studies do not show an advantage. This is an unusual situation in which high-level evidence exists but is contradictory.[105,169-171,174] The results of EBCTCG meta-analyses[175] show that radiotherapy after mastectomy and axillary node dissection reduced both recurrence and breast cancer mortality in the women with 1 to 3 positive lymph nodes even when systemic

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therapy was administered. The panel consensus for women with 1 to 3 involved ALNs and tumors greater than 5 cm or tumors with pathologic margins is that postmastectomy radiation therapy to the chest wall, infraclavicular, and supraclavicular areas should be strongly considered. The panel also recommends strong consideration of ipsilateral internal mammary field radiation therapy in these patients (category 2B).

Node-Negative Disease

Features in node-negative tumors that predict a high rate of local recurrence include primary tumors greater than 5 cm or positive pathologic margins. Chest wall irradiation is recommended for these patients.[176] Consideration should be given to radiation to the ipsilateral supraclavicular area and to the ipsilateral internal mammary lymph nodes (category 2B), especially in patients tumors greater than 5 cm, or positive surgical margins.

In patients with negative nodes, tumor less than 5 cm, and clear margins (≥1 mm), post-mastectomy radiation therapy is usually not recommended. However, the panel has noted that it may be considered only for patients with high risk of recurrence. A retrospective analysis suggests benefit of post-mastectomy radiation therapy in reducing risk of recurrence in patients with node-negative disease with high-risk factors such as close margins, tumors greater than or equal to 2 cm, premenopausal status, and lymphovascular invasion.[177] Another study showed increased risk of locoregional recurrence in women with node-negative triple-negative breast cancer with tumors less than or equal to 5 cm.[178]

Breast Reconstruction

Breast reconstruction may be an option for any woman receiving surgical treatment for breast cancer. Therefore, all women undergoing breast cancer treatment should be educated about breast reconstructive options as adapted to their individual clinical situation and be offered an opportunity to consult with a reconstructive plastic surgeon. However, breast reconstruction should not interfere with the appropriate surgical management of the cancer.

Several reconstructive approaches are summarized for these patients in the NCCN Guidelines for Breast Cancer under *Principles of Breast Reconstruction Following Surgery*.

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. Smoking and obesity increase the risk of complications for all types of breast reconstruction whether with implant or flap.[179-183] Smoking and obesity are therefore considered a relative contraindication to breast reconstruction by the NCCN Panel. Patients should be informed of increased rates of wound healing complications and partial or complete flap failure among smokers and obese patients.

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. It is sometimes necessary to perform surgery on the contralateral breast (eg, breast reduction, implantation) to achieve optimal symmetry between the ipsilateral reconstructed breast and the contralateral breast.

Breast Reconstruction After Mastectomy

Mastectomy results in loss of the breast for breastfeeding, loss of sensation in the skin of the breast and nipple-areolar complex (NAC), and loss of the breast for cosmetic, body image, and psychosocial purposes. The loss of the breast for cosmetic, body image, and psychosocial issues may be partially overcome through the

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performance of breast reconstruction with or without reconstruction of the NAC.

Many factors must be considered in the decision-making about breast reconstruction. There are several different types of breast reconstruction that include the use of implants, autogenous tissues, or both.[184-186]

Reconstruction with implants can be performed either by immediate placement of a permanent subpectoral implant or initial placement of a subpectoral expander implant followed by gradual expansion of the implant envelope with stretching of the pectoralis major muscle and overlying skin followed by replacement of the expander with a permanent implant. A wide variety of implants are available that contain saline, silicone gel, or a combination of saline and silicone gel inside a solid silicone envelope.

Autogenous tissue methods of reconstruction use various combinations of fat, muscle, skin, and vasculature from donor sites (eg, abdomen, buttock, back) that may be brought to the chest wall with their original blood supply (pedicle flap) or as free flaps with microvascular anastomoses to supply blood from the chest wall/thorax.[187] Several procedures using autologous tissue are available including transverse rectus abdominis myocutaneous flap, latissimus dorsi flap, and gluteus maximus myocutaneous flap reconstruction.

Composite reconstruction techniques use implants in combination with autogenous tissue reconstruction to provide volume and symmetry. Patients with underlying diabetes or who smoke tobacco have increased rates of complications following autogenous tissue breast cancer reconstruction, presumably because of underlying microvascular disease.

Reconstruction can be performed either at the time of the mastectomy known as “immediate breast reconstruction” and under the same anesthetic or in a delayed fashion any time, known as “delayed breast reconstruction.” In many cases, breast reconstruction involves a staged approach requiring more than one procedure such as surgery on the contralateral breast to improve symmetry, revision surgery involving the breast and/or donor site, and/or nipple and areola reconstruction and tattoo pigmentation.

Plans for post-mastectomy radiation therapy can impact decisions related to breast reconstruction since there is a significantly increased risk of implant capsular contracture following irradiation of an implant. Furthermore, postmastectomy irradiation may have a negative impact on breast cosmesis when autologous tissue is used in immediate breast reconstruction, and may interfere with the targeted delivery of radiation when immediate reconstruction is performed using either autologous tissue or breast implants.[188,189] Some studies, however, have not found a significant compromise in reconstruction cosmesis after radiation therapy.[190] The preferred approach to breast reconstruction for these patients was a subject of controversy among the panel. While some experienced breast cancer teams have employed protocols in which immediate tissue reconstructions are followed by radiation therapy, it is generally preferred that the radiation therapy precede the placement of the autologous tissue because of reported loss in reconstruction cosmesis (category 2B). When implant reconstruction is planned in a patient requiring radiation therapy after mastectomy, the NCCN Panel prefers a staged approach with immediate tissue expander placement followed by implant placement. Immediate placement of an implant in patients requiring postoperative radiation has an increased rate of capsular contracture, malposition, poor cosmesis, and implant exposure. Surgery to exchange the tissue expanders with permanent

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implants can be performed prior to radiation or after completion of radiation therapy.

In a previously radiated patient, the use of tissue expanders/implants is relatively contraindicated.[191] Tissue expansion of irradiated skin can result in a significantly increased risk of capsular contracture, malposition, poor cosmesis, implant exposure, and failed reconstruction.[192,193] If a patient has previously received radiation therapy to the breast, autologous tissue reconstruction is the preferred method of breast reconstruction.

Skin-sparing Mastectomy

Skin-sparing mastectomy procedures are appropriate for some patients and involve removal of the breast parenchyma including the NAC while preserving the majority of the original skin envelope, and are followed by immediate reconstruction with autogenous tissue, a prosthetic implant, or a composite of autogenous tissue and an implant.

Skin-sparing mastectomy involving preservation of the skin of the NAC has become the subject of increased attention. Possible advantages of this procedure include improvements in breast cosmesis, body image, and nipple sensation following mastectomy, although the impact of this procedure on these quality-of-life issues has not been well-studied.[194-196] There are limited data from surgical series, with short follow-up, that suggest that performance of NAC-sparing mastectomy in selected patients is associated with low rates of occult involvement of the NAC with breast cancer and local disease recurrence.[195,197,198] NAC-sparing procedures may be an option in patients who are carefully selected by experienced multidisciplinary teams. According to the NCCN Panel, when considering a NAC-sparing procedure, assessment of nipple margins is mandatory. Retrospective data support the use of NAC-sparing procedures for patients with breast cancer with low rates of nipple involvement and low rates of local recurrence due to early-stage, biologically favorable (eg, Nottingham grade I or 2, node-negative, HER2-negative, no lymphovascular invasion) invasive cancers and/or DCIS that are peripherally located in the breast (>2 cm from nipple).[199,200] Contraindications for nipple preservation include evidence of nipple involvement such as Paget's disease or bloody nipple discharge. Several prospective trials are underway to evaluate NAC-sparing mastectomy in the setting of cancer. Enrollment in such trials is encouraged.

Advantages of a skin-sparing mastectomy procedure include an improved cosmetic outcome resulting in a reduction in the size of the mastectomy scar and a more natural breast shape, especially when autologous tissue is used in reconstruction,[201] and the ability to perform immediate reconstruction. Although no randomized studies have been performed, results of several mostly retrospective studies have indicated that the risk of local recurrence is not increased when patients receiving skin-sparing mastectomies are compared with those undergoing non-skin–sparing procedures. However, strong selection biases almost certainly exist in the identification of patients appropriate for skin-sparing procedures.[202-206] Reconstruction of the NAC may also be performed in a delayed fashion if desired by the patient. Reconstructed nipples are devoid of sensation. According to the NCCN Panel, 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 perform a resection that achieves appropriate surgical margins. Post-mastectomy radiation should still be applied for patients treated by skin-sparing mastectomy following the same selection criteria as for standard mastectomy.

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Breast Reconstruction After Lumpectomy

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. An evaluation of the likely cosmetic outcome of lumpectomy should be performed prior to surgery. Oncoplastic techniques for breast conservation can extend breast-conserving surgical options in situations where the resection itself would likely yield an unacceptable cosmetic outcome.[207] The evolving field of oncoplastic surgery includes the use of "volume displacement" techniques performed in conjunction with a large partial mastectomy.[208] 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.[208,209]

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, and at the same time better preserve the natural shape and appearance of the breast than do standard breast resections.[210]

Limitations of oncoplastic volume displacement techniques include lack of standardization among centers, performance at only a limited number of sites in the United States, 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. Patients should be informed of the possibility of positive margins and potential need for secondary surgery, which could include re-excision segmental resection, or could require mastectomy with or without loss of the nipple. Oncoplastic procedures can be combined with surgery on the contralateral unaffected breast to minimize long-term asymmetry.

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 decision is often based on individual risk of relapse and predicted sensitivity to a particular treatment (eg, ER/PR and HER2 status).

The published results of the EBCTCG overview analyses of adjuvant chemotherapy and tamoxifen show convincing reductions in the odds of recurrence and death in all age groups for chemotherapy and endocrine therapy.[4,211] Thus, 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.[212,213]

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The decision-making process requires collaboration between the health care team and patient.

Estimating Risk of Relapse or Death and Benefits of Systemic Treatment

Several 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 ALNs, and possibly HER2 tumor status. Algorithms have been published estimating rates of recurrence,[212] and a validated, computer-based model (Adjuvant! Online; www.adjuvantonline.com) is available to estimate 10-year DFS and OS that incorporates all of the above prognostic factors except for HER2 tumor status.[213,214] 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 and benefits of systemic adjuvant therapy.[215]

A determination of the HER2 status of the tumor is recommended for prognostic purposes for patients with node-negative breast cancer. [216] More importantly, HER2 tumor status also provides 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,[217-221] and that the dose of doxorubicin may be important in the treatment of tumors that are HER2-positive.[222] Prospective evidence of the predictive utility of HER2 status in early-stage [223-228] and metastatic breast cancer[229-231] is available for trastuzumab-containing therapies.

Use of DNA microarray technologies to characterize breast cancer has allowed for development of classification systems of breast cancer by gene expression profile.[232] 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.[233-235] In retrospective analyses, these gene expression subtypes are associated with differing relapse-free survival and OS.

There are many gene-based assays to predict prognosis such as distant recurrence, local recurrence, or survival.

The 21-gene assay using reverse transcription polymerase chain reaction (RT-PCR) on RNA isolated from paraffin-embedded breast cancer tissue (Oncotype DX) is among the best-validated prognostic assays, and there are data showing that it can predict who is most likely to respond to systemic chemotherapy.

Studies have shown that the 21-gene recurrence score obtained is predictive of locoregional and distant recurrence for postmenopausal women treated with tamoxifen or those treated with an aromatase inhibitor.[236-238] Studies have also demonstrated the ability of the recurrence score to independently predict response to adjuvant chemotherapy.[239-241] Unplanned, retrospective subset analysis from a single randomized clinical trial in post-menopausal, ALN-positive, ER-positive breast cancer found that the 21-gene RT-PCR assay may provide predictive information for chemotherapy benefit in addition to tamoxifen.[239] Patients with a high score in the study benefited from

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chemotherapy, whereas patients with a low score did not appear to benefit from the addition of chemotherapy regardless of the number of positive lymph nodes.[239] Many other multi-gene or multi-gene expression assay systems have been developed. MammaPrint assay uses microarray technology to analyze a 70-gene expression profile from breast tumor tissue (formalin-fixed, paraffin-embedded fresh or frozen breast tumor tissue) to help identify patients with early-stage breast cancer likely to develop distant metastases.[242-248] MammaPrint is approved by the FDA to assist in assignment of women with ER-positive or ER-negative breast cancer into a high versus low risk for recurrence, but not for predicting benefit from adjuvant systemic therapy. MammaPrint is approved by the FDA and assigns women of all ages with ER-positive or ER-negative breast cancer as having high versus low risk for recurrence. The prospective RASTER study reported that breast cancer patients classified by MammaPrint as low risk (of whom 85% did not receive adjuvant chemotherapy) had an overall 97% distant recurrence-free interval at five years.[249]

The Prediction Analysis of Microarray 50 (PAM50) is a 50-gene test that identifies intrinsic breast cancer subtypes (luminal A, luminal B, HER2 enriched and basal-like) in addition to generating a risk of recurrence (ROR) score that can be used to predict prognosis among postmenopausal women with hormone-positive breast cancer. In an analysis of the ATAC trial[250] of postmenopausal patients treated with adjuvant tamoxifen or anastrozole, the ROR score obtained using the PAM50 assay was seen to have a continuous relationship with the risk of distant recurrence at 10 years in both node-negative and node-positive disease. In the same retrospective analysis, the ROR score obtained using PAM50 was compared with the recurrence score obtained using Oncotype DX for its ability to stratify patients with hormone receptor-positive, node-negative breast cancer. Both assays identified similar percentage of low-risk patients with similar risk of recurrence.

The NCCN Panel members acknowledge that many assays, including PAM50 and MammaPrint, have been clinically validated for prediction of prognosis. However, based on the currently available data, the panel believes that the 21-gene assay has been best-validated for its use as a prognostic test as well as in predicting who is most likely to respond to systemic chemotherapy,

Patients with a high recurrence score (obtained using the 21-gene assay) benefit from chemotherapy, whereas patients with a low score do not appear to benefit from the addition of chemotherapy regardless of the number of positive lymph nodes.[239] The additional benefit from adjuvant chemotherapy in addition to endocrine therapy is currently unclear for intermediate-risk patients (as assessed by the gene-based assays). The TAILORx and RxPONDER trials are being conducted to help answer this question. In the TAILORx trial, patients with node-negative, hormone receptor-positive breast cancer classified as being at low risk based on the gene signature or Adjuvant! Online are receiving endocrine therapy alone, whereas patients deemed to be at high risk based on gene signature profiles or other characteristics are receiving chemotherapy in addition to endocrine therapy. Those classified with an intermediate risk are being randomized to receive chemotherapy or no chemotherapy.[251] The RxPONDER trial will attempt to confirm the SWOG-8814 trial data for women with ER-positive, node-positive disease treated with endocrine therapy with or without chemotherapy based on risk scores.[252] The findings from these trials will help determine the benefit of treating patients at intermediate risk with adjuvant chemotherapy. The MINDACT trial is comparing the 70-gene signature with the commonly used clinicopathologic criteria in selecting patients for adjuvant chemotherapy in breast cancer with 0 to 3 positive

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nodes.[253] The findings from this trial will help determine the prognostic value of MammaPrint and the benefit of treating intermediate-risk patients with adjuvant chemotherapy.

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. According to the NCCN Panel, endocrine therapy may be considered to reduce the risk for 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 endocrine therapy is not an effective strategy to reduce the risk for contralateral breast cancer in patients diagnosed with ER-negative tumors.[254]

Patients with invasive ductal or lobular tumors greater than or equal to 5 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 histologic grade, HER2-positive status, or hormone receptor-negative status. 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.

For women with lymph node-negative, hormone receptor-*negative* tumors less than or equal to 0.5 cm with micrometastasis (pN1mi) or tumors 0.6 to 1.0 cm, the NCCN Guidelines suggest considering adjuvant chemotherapy (category 2A). For tumors greater than 1 cm in diameter chemotherapy is a category 1 recommendation.

For those with lymph node-negative, hormone receptor-positive breast cancer tumors greater than 0.5 cm, the panel recommends endocrine therapy (category 1) with the consideration of chemotherapy. Incremental benefit of combination chemotherapy in patients with lymph node-negative, hormone receptor-positive breast cancer may be relatively small.[255] However, chemotherapy should not be withheld from these patients solely based on ER-positive tumor status.[4,255,256] The panel considers the 21-gene RT-PCR assay an option for these patients to help estimate likelihood of recurrence *and* benefit from chemotherapy. 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.

Axillary Lymph Node-Positive Tumors

Patients with lymph node-positive disease are most often candidates for chemotherapy and, if the tumor is hormone receptor-positive, for the addition of endocrine therapy (category 1). When HER2 is amplified or over-expressed, HER2 targeted therapy should be incorporated into the adjuvant chemotherapy. The NCCN Panel has noted in a footnote that the 21-gene RT-PCR assay recurrence score can be considered in select patients with 1 to 3 involved ipsilateral ALNs to guide the addition of combination chemotherapy to standard hormone therapy based on the retrospective study by Albain et al.[239]

Stratification for Systemic Adjuvant Therapy

The NCCN Guidelines stratify patients with breast cancer based on their hormone receptor status and HER2 expression. Patients are then further stratified based on risk of disease recurrence based on anatomic

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and pathologic characteristics (ie, tumor grade, tumor size, ALN status, angiolymphatic invasion).

Adjuvant Endocrine Therapy

The NCCN Guidelines call for the determination of ER and PR content in all primary invasive breast cancers.[15] 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 adjuvant chemotherapy is to be administered.[257] 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.[219,258-265] A retrospective analysis of tumor blocks collected in the ATAC trial indicated that HER2 amplification is a marker of relative endocrine resistance independent of type of endocrine therapy.[266] 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.

Tamoxifen

The most firmly established adjuvant endocrine therapy is tamoxifen for both premenopausal and postmenopausal women.[4] 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 ALN status.[4] In patients receiving both tamoxifen and chemotherapy, chemotherapy should be given first, followed by sequential tamoxifen.[256] Prospective randomized trials have demonstrated that 5 years of tamoxifen is more effective than 1 to 2 years of tamoxifen.[267,268]

The ATLAS trial randomly allocated 12,894 women to continue tamoxifen up to 10 years or to discontinue tamoxifen (control). The outcome analyses of 6846 women with ER-positive disease showed that by extending adjuvant treatment to 10 years, the risk of relapse and breast cancer-related mortality was reduced.[269] The risk of recurrence during years 5 to 14 was 21.4% for women receiving tamoxifen versus 25.1% for controls (absolute recurrence reduction 3.7%). Patients receiving tamoxifen beyond 10 years of treatment had a greater reduction in risk of progression, possibly due to a “carryover effect.” The reduction in risk of recurrence was 0.90 (95% CI, 0.79–1.02) during 5 to 9 years of tamoxifen treatment and 0.75 (0.62–0.90) after 10 years. Furthermore, reduced mortality was apparent after completion of 10 years of treatment with tamoxifen. With regards to toxicity, the most important adverse effects noted in all women in the ATLAS trial were an increased risk for endometrial cancer after treatment with 10 years of tamoxifen and pulmonary embolism. The recurrence rate ratios for incidence of adverse events (hospitalization or death) were: pulmonary embolus 1.87 (95% CI, 1.13–3.07, P = .01 [including 0.2% mortality in both treatment groups]), stroke 1.06 (0.83–1.36), ischemic heart disease 0.76 (0.60–0.95, P = .02), and endometrial cancer 1.74 (1.30–2.34, P = .0002). The cumulative risk for endometrial cancers during 5 to 14 years was 3.1%, with a mortality of 0.4% associated with endometrial cancer, higher than what was noted in the control group of patients receiving only 5 years of therapy (cumulative risk: 1.6%; mortality: 0.2%).[269] The results of the aTTom trial confirm the ATLAS reduction in recurrence and death from breast cancer.[270]

In women who are premenopausal at diagnosis, the NCCN Panel recommends tamoxifen treatment with or without ovarian suppression/ablation. Ovarian ablation may be accomplished by surgical oophorectomy or by ovarian irradiation. Ovarian suppression

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utilizes luteinizing hormone-releasing hormone (LHRH) agonists that result in suppression of luteinizing hormone (LH) and release of follicle-stimulating hormone (FSH) from the pituitary and reduction in ovarian estrogen production. Available LHRH agonists in the United States include goserelin and leuprolide and, when used for ovarian suppression, both agents should be given as monthly injections as the 3-month depots do not reliably suppress estrogen levels in all patients.

The EBCTCG performed a meta-analysis of randomized studies of ovarian ablation or suppression alone versus no additional systemic adjuvant therapy for early-stage breast cancer.

Analysis of ovarian suppression versus no adjuvant therapy did not demonstrate significant reduction in recurrence (0.72, 95% CI, 0.49–1.04) or death (HR 0.82, 95% CI, 0.47–1.43).[271] In addition, data on ovarian suppression with tamoxifen, chemotherapy, or both showed no significant reduction in reduced recurrence or death.

Studies in premenopausal women of ovarian ablation or suppression alone versus CMF (cyclophosphamide/methotrexate/fluorouracil) chemotherapy alone generally demonstrate similar antitumor efficacy in patients with hormone receptor-positive tumors and superior outcomes with CMF in patients with hormone receptor-negative tumors.[271-279] There is also the suggestion that the benefits of ovarian suppression/ablation may be greater in the younger premenopausal group. Studies in premenopausal women of ovarian ablation/suppression plus tamoxifen versus chemotherapy alone generally demonstrate no difference in rates of recurrence or survival.[280-282]

A large intergroup study in premenopausal women with hormone receptor-positive, node-positive breast cancer studied adjuvant CAF (cyclophosphamide/doxorubicin/5-fluorouracil) chemotherapy versus CAF plus ovarian suppression with goserelin (CAF-Z) versus CAF-Z plus tamoxifen (CAF-ZT).[272] The results demonstrated no improvement in time to recurrence or OS comparing CAF with CAF-Z. There was improvement in time to recurrence (HR, 0.73; 95% CI, 0.59–0.90; $P <$ .01) but not OS with CAF-Z compared with CAF-ZT (HR, 0.91; 95% CI, 0.71–1.15; $P = .21$). This study did not include a CAF plus tamoxifen arm, so the contribution of the goserelin to the improved time to recurrence in the CAF-ZT arm cannot be assessed. The addition of ovarian suppression/ablation has also been subjected to meta-analysis by the EBCTCG.[280] They identified no statistically significant reduction in annual rates of recurrence or death with the addition of ovarian suppression or ablation to chemotherapy in women less than 40 years or 40 to 49 years of age.

In two randomized trials (TEXT and SOFT), premenopausal women with hormone receptor-positive early-stage breast cancer were assigned to receive exemestane plus ovarian suppression or tamoxifen plus ovarian suppression for a period of 5 years.[283] Suppression of ovarian estrogen production was achieved with the use of the gonadotropin-releasing-hormone agonist triptorelin, oophorectomy, or ovarian irradiation. The DFS was 92.8% in the exemestane plus ovarian suppression group, as compared with 88.8% in the tamoxifen plus ovarian suppression group (HR for recurrence, 0.66; 95% CI, 0.55–0.80; $P < .001$).[283] The OS did not differ significantly between the two groups (HR for death in the exemestane plus ovarian suppression group, 1.14; 95% CI, 0.86–1.51; $P = .37$).[283] Women at high risk of recurrence who received prior chemotherapy had improved outcomes with ovarian suppression. Their chance of remaining disease-free at 5 years was 78% with tamoxifen alone, 82.5% with tamoxifen and ovarian suppression, and 85.7% with exemestane and ovarian suppression. In

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the cohort of women with no prior chemotherapy, no meaningful benefit was seen from ovarian suppression, as women who received tamoxifen alone demonstrated a 95% chance of remaining disease-free for 5 years.

Several studies have evaluated aromatase inhibitors in the treatment of postmenopausal women with early-stage breast cancer. These studies have utilized the aromatase inhibitors as initial adjuvant therapy, as sequential therapy following 2 to 3 years of tamoxifen, or as extended therapy following 4.5 to 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 reliably be assessed owing to treatment-induced amenorrhea. The results from two prospective, randomized, clinical trials have provided evidence of an OS benefit for patients with early-stage breast cancer receiving initial endocrine therapy with tamoxifen followed sequentially by anastrozole (HR, 0.53; 95% CI, 0.28–0.99; *P* = .045) or exemestane (HR, 0.83; 95% CI, 0.69–1.00; *P* = .05 [excluding patients with ER-negative disease]) when compared with tamoxifen as the only endocrine therapy.[284,285] In addition, the NCIC-CTG MA-17 trial demonstrated a survival advantage with extended therapy with letrozole compared with placebo in women with ALN-positive (but not lymph node-negative), ER-positive breast cancer.[286] However, no survival differences have been reported for patients receiving initial adjuvant therapy with an aromatase inhibitor versus first-line tamoxifen.[287,288] Tamoxifen and aromatase inhibitors have different side effect profiles. Both contribute to hot flashes and 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 for 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.[289,290] With a median of 100 months follow-up, results in 5216 postmenopausal women with hormone receptor-positive, early-stage breast cancer enrolled in the ATAC trial demonstrated fewer recurrences (HR for DFS, 0.85; 95% CI, 0.76–0.94; *P* = .003) with anastrozole compared with tamoxifen.[287] No difference in survival has been observed (HR, 0.90; 95% CI, 0.75–1.07; *P* = .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.[290] ATAC trial sub-protocols show a lesser effect of anastrozole compared with tamoxifen on endometrial tissue;[291] similar effects of anastrozole and tamoxifen on quality of life, with most patients reporting that overall quality of life was not significantly impaired;[292] a greater loss of bone mineral density with anastrozole;[293] a small pharmacokinetic interference of anastrozole in the presence of tamoxifen of unclear significance;[294] and no evidence for an interaction between prior chemotherapy and anastrozole.[295]

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 2 years of treatment only.[288] With 8010 women included in the analysis, DFS was superior in the

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letrozole-treated women (HR, 0.81; 95% CI, 0.70– 0.93; log rank *P* = .003). No interaction between PR expression and benefit was observed. No difference in OS was observed. A comparison of the cardiovascular side effects in the tamoxifen and letrozole arms 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.[296] In addition, a higher incidence of bone fracture was observed for women in the letrozole arm compared with those in the tamoxifen arm (9.5% vs. 6.5%).[297] After a longer follow-up (median 71 months) no significant improvement in DFS was noted with either tamoxifen followed by letrozole or the reverse sequence as compared with letrozole alone (HR for tamoxifen followed by letrozole, 1.05; 99% CI, 0.84–1.32; HR for letrozole followed by tamoxifen, 0.96; 99% CI, 0.76–1.21).[298]

Five trials have studied the use of tamoxifen for 2 to 3 years followed sequentially by a third-generation aromatase inhibitor versus continued tamoxifen in postmenopausal women. The Italian Tamoxifen Anastrozole (ITA) trial randomized 426 postmenopausal women with breast cancer who had completed 2 to 3 years of tamoxifen to either continue tamoxifen or to switch to anastrozole to complete a total of 5 years of endocrine therapy.[299] The HR for relapse strongly favored sequential treatment with anastrozole (HR, 0.35; 95% CI, 0.18–0.68; *P* = .001) with a trend towards fewer deaths (*P* = .10).[299] Updated results from this study show the HR for relapse-free survival as 0.56 (95% CI, 0.35–0.89; *P* = .01); P value for OS analysis remained at 0.1.[300] The IES trial randomized 4742 postmenopausal women with breast cancer who had completed a total of 2 to 3 years of tamoxifen to either continue tamoxifen or to switch to exemestane to complete a total of 5 years of endocrine therapy.[301] The results at a median of 55.7 months of follow-up demonstrated the superiority of sequential exemestane in DFS (HR, 0.76; 95% CI, 0.66–0.88; *P* = .0001) with a significant difference in OS in only patients with ER-positive tumors (HR, 0.83; 95% CI, 0.69–1.00; log rank *P* = .05). A prospectively planned, combined analysis of 3224 patients enrolled in the ABCSG 8 trial and the Arimidex Nolvadex (ARNO 95) trial has also been reported.[302] Patients in this combined analysis had been randomized following 2 years of tamoxifen to complete 5 years of adjuvant tamoxifen or 3 years of anastrozole. With 28 months of median follow-up available, event-free survival was superior with crossover to anastrozole (HR, 0.60; 95% CI, 0.44–0.81; *P* = .0009). No statistically significant difference in survival has been observed. An analysis of the ARNO 95 trial alone after 58 months of median follow-up demonstrated that switching from tamoxifen to anastrozole was associated with significant increases in both DFS (HR, 0.66; 95% CI, 0.44–1.00; *P* = .049) and OS (HR, 0.53; 95% CI, 0.28–0.99; *P* = .045).[285] A meta-analysis of ABCSG 8, ARNO 95, and ITA studies showed significant improvement in OS (HR, 0.71; 95% CI, 0.52-0.98; *P* = .04) with a switch to anastrozole.[303]

The TEAM trial compared treatment of exemestane alone versus sequential therapy of tamoxifen for 2.5 to 3.0 years followed by exemestane to complete 5 years of hormone therapy.[304] At the end of 5 years, 85% of patients in the sequential group versus 86% in the exemestane group were disease free (HR, 0.97; 95% CI, 0.88–1.08; *P* = .60). This is consistent with the data from the BIG 1-98 trial,[298] in which tamoxifen followed by letrozole or the reverse sequence of letrozole followed by tamoxifen was not associated with significant differences in efficacy versus letrozole monotherapy after a median follow-up of 71 months.

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Results of the MA-17 trial in 5187 women who had completed 4.5 to 6 years of adjuvant tamoxifen demonstrated that extended therapy with letrozole provides benefit in postmenopausal women with hormone receptor-positive, early-stage breast cancer.[286,305] At a median follow-up of 2.5 years, the results showed fewer recurrences or new contralateral breast cancers with extended letrozole (HR, 0.58; 95% CI, 0.45– 0.76; *P* < .001). No difference in OS was demonstrated (HR, 0.82; 95% CI, 0.57–1.19; *P* = .3), although there was a survival advantage in the subset of patients with ALN-positive disease (HR 0.61; 95% CI, 0.38–0.98; *P* = .04). In a separate cohort analysis of the MA-17 trial, the efficacy of letrozole versus placebo was evaluated after un-blinding of the study in the 1579 women who had been randomly assigned to placebo after 4.5 to 6 years of tamoxifen.[306,307] The median time since completion of tamoxifen was 2.8 years. Both DFS and distant DFS were significantly improved in the group receiving letrozole, thereby providing some evidence for the efficacy of letrozole in patients who had received 4.5 to 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.[308,309] No data are available regarding use of aromatase inhibitors for more than 5 years or long-term toxic effects from extended treatment. In addition, the ATLAS trial data do not provide clear direction for treatment of postmenopausal women.[310] There are no data available to suggest that an aromatase inhibitor for 5 years is better for long-term benefit than 10 years of tamoxifen.

In the extension study of ABCSG trial 6, hormone receptor-positive postmenopausal patients received 5 years of adjuvant tamoxifen and were randomized to 3 years of anastrozole or no further therapy.[311] At a median follow-up of 62.3 months, women who received anastrozole (n = 387) were reported to have a statistically significantly reduced risk of recurrence compared with women who received no further treatment (n = 469; HR, 0.62; 95% CI, 0.40–0.96; *P* = .031).[311]

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. A meta-analysis of adjuvant trials of aromatase inhibitors versus tamoxifen alone versus after 2 or 3 years of tamoxifen documented lower recurrence rates with the aromatase inhibitor-containing regimen, with no clear impact on OS.[312] 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 recurrences, contralateral breast cancer, and distant metastatic disease when used as initial adjuvant therapy, sequential therapy, or extended therapy. The panel finds no compelling evidence that there is meaningful efficacy or toxicity differences between the aromatase inhibitors, anastrozole, letrozole, and exemestane. All three have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant settings.

NCCN recommendations for adjuvant endocrine therapy for postmenopausal women: The NCCN Guidelines for Breast Cancer recommend the following adjuvant endocrine therapy options for women

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with early-stage breast cancer who are postmenopausal at diagnosis: an aromatase inhibitor as initial adjuvant therapy for 5 years (category 1); tamoxifen for 2 to 3 years followed by one of the following options: an aromatase inhibitor to complete 5 years of adjuvant endocrine therapy (category 1) or 5 years of aromatase inhibitor therapy (category 2B); or tamoxifen for 4.5 to 6 years followed by 5 years of an aromatase inhibitor (category 1) or consideration of tamoxifen for up to 10 years. In postmenopausal women, the use of tamoxifen alone for 5 years (category1) or up to 10 years is limited to those who decline or who have a contraindication to aromatase inhibitors.

NCCN recommendations for adjuvant endocrine therapy for premenopausal women: For women premenopausal at diagnosis, the NCCN Guidelines for Breast Cancer recommend 5 years of tamoxifen (category 1) with or without ovarian suppression (category 2B). The NCCN Panel has noted in a footnote that ovarian suppression plus an aromatase inhibitor for 5 years may be considered as an option for premenopausal women. Women who are premenopausal at diagnosis and who become amenorrheic with chemotherapy may have continued estrogen production from the ovaries without 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.[313,314]

After 5 years of initial endocrine therapy, for women who are postmenopausal at that time (including those who have become postmenopausal during the 5 years of tamoxifen therapy), the NCCN Panel recommends considering extended therapy with an aromatase inhibitor for up to 5 years (category 1) or based on the data from the ATLAS trial considering tamoxifen for an additional 5 years. For those who remain premenopausal after the initial 5 years of tamoxifen, the panel recommends considering continuing up to 10 years of tamoxifen therapy.

Response to adjuvant endocrine therapy: The measurement of the nuclear antigen, Ki-67 by IHC, gives an estimate of the tumor cells in the proliferative phase (G1, G2, and M phases) of the cell cycle. Studies have demonstrated the prognostic value of Ki-67 as a biomarker and its usefulness in predicting response and clinical outcome.[315] One small study suggests that measurement of Ki-67 after short-term exposure to endocrine treatment may be useful to select patients with tumors resistant to endocrine therapy and those who may benefit from additional interventions.[316] However, these data require larger analytic and clinical validation. In addition, standardization of tissue handling and processing is required to improve the reliability and value of Ki-67 testing. At this time, there is no conclusive evidence that Ki-67 alone, especially baseline Ki-67 as an individual biomarker, helps to select the type of endocrine therapy for an individual patient. Therefore, the NCCN Breast Cancer Panel does not currently recommend assessment of Ki-67.

The cytochrome P-450 (CYP450) enzyme, CYP2D6, is involved in the conversion of tamoxifen to endoxifen. Over 100 allelic variants of *CYP2D6* have been reported in the literature.[317] Individuals with wild-type *CYP2D6* alleles are classified as extensive metabolizers of tamoxifen. Those with one or two variant alleles with either reduced or no activity are designated as intermediate metabolizers and poor metabolizers, respectively. A large retrospective study of 1325 patients found that time to disease recurrence was significantly shortened in poor metabolizers of tamoxifen.[318] However, the BIG 1-98 trial reported on the outcome based on CYP2D6 genotype in a subset of postmenopausal patients with endocrine-responsive, early invasive

breast cancer.[319] The study found no correlation between CYP2D6 allelic status and disease outcome or between CYP2D6 allelic status and tamoxifen-related adverse effects.[319] A genetic analysis of the ATAC trial found no association between CYP2D6 genotype and clinical outcomes.[320] Given the limited and conflicting evidence at this time,[321] the NCCN Breast Cancer Panel does not recommend CYP2D6 testing as a tool to determine the optimal adjuvant endocrine strategy. This recommendation is consistent with the ASCO Guidelines.[322] When prescribing a selective serotonin reuptake inhibitor (SSRI), it is reasonable to avoid potent and intermediate CYP2D6 inhibiting agents, particularly paroxetine and fluoxetine, if an appropriate alternative exists.

Adjuvant Cytotoxic Chemotherapy

Several combination chemotherapy regimens are appropriate to consider when adjuvant cytotoxic chemotherapy is utilized. All adjuvant chemotherapy regimens listed in the NCCN Guidelines have been evaluated in phase III clinical trials, and the current version of the adjuvant chemotherapy guidelines does not distinguish between options for chemotherapy regimens by ALN status.

The adjuvant chemotherapy guidelines also include specific representative doses and schedules for the recommended adjuvant chemotherapy regimens. The regimens have been categorized as "preferred" or "other."

The purpose of distinguishing the adjuvant chemotherapy regimens as preferred and other adjuvant chemotherapy regimens is to convey the sense of the panel regarding the relative efficacy and toxicity of the regimens.[323] Factors considered by the panel include the efficacy, toxicity, and treatment schedules of the regimens. Summarized below are clinical trial results focusing on treatment efficacy.

Preferred Regimens

Regimens listed as preferred include: dose-dense doxorubicin and cyclophosphamide (AC) with dose-dense sequential paclitaxel; dose-dense AC followed by sequential weekly paclitaxel; and docetaxel plus cyclophosphamide (TC).

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 OS, with the addition of paclitaxel.[324,325] 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 vs. doxorubicin plus cyclophosphamide followed by paclitaxel) given either every 2 weeks with filgrastim support or every 3 weeks. The results show no significant difference between the two chemotherapy regimens, but demonstrate a 26% reduction in hazard of recurrence (P = .01) and a 31% reduction in the hazard of death (P = .013) for the dose-dense regimens.[326]

The ECOG E1199 study was a four-arm trial that randomized 4950 women to receive AC chemotherapy followed by either paclitaxel or docetaxel given by either an every-3-week schedule or a weekly schedule.[327-329] At a median 63.8 months of follow-up, no statistically significant differences in DFS or OS were observed when comparing paclitaxel to docetaxel or weekly versus every-3-week administration. In a secondary series of comparisons, weekly paclitaxel was superior to every-3-week paclitaxel in DFS (HR, 1.27; 95% CI, 1.03–1.57; P = .006) and OS (HR, 1.32; 95% CI, 1.02–1.72; P = .01), and every-3-week

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docetaxel was superior to every-3-week paclitaxel in DFS (HR, 1.23; 95% CI, 1.00–1.52; *P* = .02) but not in OS.[329] Based on these results, as well as the findings from the CALGB trial 9741 that showed dose-dense AC followed by paclitaxel every 2 weeks to have a survival benefit when compared with the regimen of AC followed by every-3-week paclitaxel,[326] the every-3-week paclitaxel regimen has been removed from the guidelines.

Combination TC was compared with AC chemotherapy in a trial that randomized 1016 women with stage I to III breast cancer.[330] At a median follow-up of 7 years, overall DFS (81% vs. 75%; HR, 0.74; 95% CI, 0.56–0.98; *P* = .033) and OS (87% vs. 82%; HR, 0.69; 95% CI, 0.50–0.97; *P* = .032) were significantly improved with TC compared with AC.

Other Regimens

Other regimens included in the guidelines are: AC; fluorouracil, doxorubicin, and cyclophosphamide (FAC/CAF); cyclophosphamide, epirubicin, and fluorouracil (FEC/CEF); epirubicin and cyclophosphamide (EC); CMF; AC with sequential docetaxel administered every 3 weeks; AC with sequential weekly paclitaxel; FEC/CEF followed by docetaxel or weekly paclitaxel; FAC followed by weekly paclitaxel; and docetaxel, doxorubicin, and cyclophosphamide (TAC).

The AC regimen for four cycles has been studied in randomized trials, resulting in relapse-free survival and OS equivalent to CMF chemotherapy.[331,332] No benefit from dose escalation of either doxorubicin or cyclophosphamide was shown.[324,333]

Studies of CMF chemotherapy versus no chemotherapy have shown DFS and OS advantages with CMF chemotherapy.[4,334] Studies using FAC/CAF chemotherapy have shown that the use of full-dose chemotherapy regimens is important.[335] In the EBCTCG overview of polychemotherapy, comparison of anthracycline-containing regimens with CMF showed a 12% further reduction in the annual odds of recurrence (*P* = .006) and an 11% further reduction in the annual odds of death (*P* = .02) with anthracycline-containing regimens.[334] 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 EBCTCG 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.[216,218,221,263,336-338] 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.

A trial compared 2 dose levels of EC chemotherapy with CMF chemotherapy in women with node-positive breast cancer.[339] This study showed that higher-dose EC chemotherapy was equivalent to CMF chemotherapy and superior to moderate-dose EC in event-free survival and OS.

Two randomized prospective trials of FEC chemotherapy in ALN-positive breast cancer are available. In one trial, premenopausal women with node-positive breast cancer were randomized to receive

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classic CMF therapy versus FEC chemotherapy using high-dose epirubicin. Both 10-year relapse-free survival (52% vs. 45%; *P* = .007) and OS (62% vs. 58%; *P* = .085) favored the FEC arm of the trial.[340] The second trial compared FEC given 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 DFS (55% vs. 66%; *P* = .03) and OS (65% vs. 76%; *P* =.007) both favored the epirubicin 100 mg/m^2 arm.[341] Another randomized trial in women with ALN-positive breast cancer compared 6 cycles of FEC with 3 cycles of FEC followed by 3 cycles of docetaxel.[281] Five-year DFS (78.4% vs. 73.2%; adjusted *P* = .012) and OS (90.7% vs. 86.7%; *P* = .017) were superior with sequential FEC followed by docetaxel. However, no significant DFS differences were seen in a large randomized study comparing adjuvant chemotherapy with 4 cycles of every-3-week FEC followed by 4 cycles of every-3-week docetaxel with standard anthracycline chemotherapy regimens (eg, FEC or epirubicin followed by CMF) in women with node-positive or high-risk, node-negative, operable breast cancer.[342]

The addition of weekly paclitaxel following FEC was shown to be superior to FEC alone in a randomized study of 1246 women with early-stage breast cancer.[343] The former regimen was associated with a 23% reduction in the risk of relapse compared with FEC (HR, 0.77; 95% CI, 0.62–0.95; *P* = .022), although no significant difference in OS was seen when the two arms were compared at a median follow-up of 66 months.

The NSABP B-36 trial compared standard adjuvant chemotherapy 4 cycles of AC every 3 weeks with 6 cycles of FEC every 3 weeks in patients with node-negative breast cancer. The 8-year DFS and OS were similar in both arms. Toxicities were higher with the FEC regimen, and there were 5 deaths in the FEC arm compared to 2 deaths in the standard therapy group.[344]

The phase III E1199 trial compared patients with node-positive or high-risk node-negative breast cancer who received 4 cycles of AC every 3 weeks, followed by either paclitaxel or docetaxel, either weekly or every 3 weeks. The 10-year updated results of this trial showed that incorporation of weekly paclitaxel and docetaxel every 3 weeks was associated with significant improvements in DFS, and marginal improvements in OS, compared with paclitaxel given every 3 weeks. Among patients with triple-negative disease, the10-year DFS rate with weekly paclitaxel was 69% and the 10-year OS rate was 75%.[345]

Final results from a randomized trial of TAC versus FAC chemotherapy in ALN-positive breast cancer demonstrated that TAC is superior to FAC.[346] Estimated 5-year DFS was 75% with TAC and 68% with FAC (HR, 0.72; 95% CI, 0.59–0.88; *P* =.001); survival was 87% with TAC and 81% with FAC (HR, 0.70; 95% CI, 0.53–0.91; *P* = .008). DFS favored TAC in both ER-positive and ER-negative tumors. At a median follow-up of 73 months, results from the 3-arm randomized NSABP B-30 trial comparing TAC versus AT versus AC followed by docetaxel (AC followed by T) demonstrated that AC followed by T had a significant advantage in DFS (HR, 0.83; *P* = .006) but not in OS (HR, 0.86; *P* = .086) when compared with TAC. In addition, both DFS (HR, 0.080; *P* = .001) and OS (HR, 0.83; *P* = .034) were significantly increased when AC followed by T was compared with AT, with AT demonstrating non-inferiority compared with TAC.[347]

Several retrospective studies have evaluated the potential interaction of chemotherapy benefit and ER status.[4,255] These studies assessed the effect of chemotherapy on the risk of breast cancer recurrence in patients with ER-positive tumors receiving adjuvant endocrine therapy

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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.[255]

For women greater than 70 years of age, the consensus of the panel is that there are insufficient data to make definitive chemotherapy recommendations. Although AC or CMF has been shown to be superior to capecitabine in a randomized trial of women aged greater than or equal to 65 years with early-stage breast cancer,[348] the enrollment in that study was discontinued early.[348] Therefore there is also a possibility that AC/CMF is not superior to any chemotherapy in this cohort. The panel recommends that treatment should be individualized for women in this age group, with consideration given to comorbid conditions.

Adjuvant HER2-Targeted Therapy

The panel recommends HER2-targeted therapy in patients with HER2-positive tumors (see *Principles of HER2 Testing*). Trastuzumab is a humanized monoclonal antibody with specificity for the extracellular domain of HER2.[349]Results of several randomized trials testing trastuzumab as adjuvant therapy have been reported.[223-228,350-352]

NSABP B-31 patients with HER2-positive, node-positive breast cancer were randomly assigned to 4 cycles of AC every 3 weeks followed by paclitaxel for 4 cycles every 3 weeks or the same regimen with 52 weeks of trastuzumab commencing with paclitaxel. In the NCCTG N9831 trial, patients with HER2-positive breast cancer that was node-positive, or 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 have been jointly analyzed with the merged control arms for both trials compared with the merged arms using trastuzumab begun concurrently with paclitaxel. There were 4045 patients included in the joint analysis performed at 3.9 years median follow-up. A 48% reduction in the risk of recurrence (HR, 0.52; 95% CI, 0.45–0.60; $P < .001$) and a 39% reduction in the risk of death (HR, 0.61; 95% CI, 0.50–0.75; log-rank $P = .001$) were documented.[351] Similar significant effects on DFS 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.[226,353,354] In the adjuvant trastuzumab trials, the rates of grade III/IV congestive heart failure (CHF) or cardiac-related death in patients receiving treatment regimens containing trastuzumab ranged from 0% (FinHer trial) to 4.1% (NSABP B-31 trial).[223,224,226,228,353,354] 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 CHF 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.[353] 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.[355,356]

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A third trial (HERA) (N = 5081) tested trastuzumab for 1 or 2 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 greater than or equal to 1 cm.[224] At a median follow-up of one year, a 46% reduction in the risk of recurrence was reported in those who received trastuzumab compared with those who did not (HR, 0.54; 95% CI, 0.43–0.67; *P* < .0001), there was no difference in OS, and acceptable cardiac toxicity was reported. The 2-year data indicate that 1 year of trastuzumab therapy is associated with an OS benefit when compared with observation (HR for risk of death = 0.66; 95% CI, 0.47–0.91; *P* = .0115).[357] After this initial analysis, patients randomized to chemotherapy alone were allowed to cross over to receive trastuzumab. Intent-to-treat analysis including a crossover patient was reported at 4-year median follow-up.[352] The primary endpoint of DFS continued to be significantly higher in the trastuzumab-treated group (78.6%) versus the observation group (72.2; HR, 0.76; 95% CI, 0.66–0.87; *P* < .0001). At a median follow-up of 8 years, the study reported no significant difference in DFS, a secondary endpoint, in patients treated with trastuzumab for 2 years compared with 1 year.[225] Therefore, 1 year of adjuvant trastuzumab remains the current standard of treatment.

The BCIRG 006 study randomized 3222 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, and trastuzumab for one year.[228] At 65-month follow-up, patients receiving AC followed by docetaxel with trastuzumab (AC-TH) had an HR for DFS of 0.64 (*P* < .001) when compared with the group of patients in the control arm receiving the same chemotherapy regimen without trastuzumab (AC-T). The HR for DFS was 0.75 (*P* = .04) when patients in the carboplatin/docetaxel/ trastuzumab (TCH)-containing arm were compared to patients in the control arm. No statistically significant difference in the HR for DFS was observed between the two trastuzumab-containing arms. An OS advantage was reported for patients in both trastuzumab-containing arms relative to the control arm (HR for AC-TH vs. AC-T = 0.63; *P* = .001; HR for TCH vs. AC-T = 0.77; *P* = .04). Cardiac toxicity was significantly lower in the TCH arm (9.4% patients with >10% relative decline in left ventricular ejection fraction) compared with the AC-TH arm (18.6%; *P* < .0001). CHF was also more frequent with AC-TH than TCH (2% vs. 0.4%; *P* < .001). Analysis of this trial by critical clinical event revealed more distant breast cancer recurrences with TCH (144 vs. 124) but fewer cardiac events with TCH compared with AC-TH (4 vs. 21).[228] In the FinHer trial, 1010 women were randomized to 9 weeks of vinorelbine followed by 3 cycles of FEC chemotherapy versus docetaxel for 3 cycles followed by 3 cycles of FEC chemotherapy.[223] Patients (n = 232) with HER2-positive cancers that were either node-positive or node-negative and greater than or equal to 2 cm and PR-negative were further randomized to receive or not receive 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 (HR, 0.42; 95% CI, 0.21–0.83; *P* = .01). No statistically significant differences in OS (HR, 0.41; 95% CI, 0.16–1.08; *P* = .07) or cardiac toxicity were observed with the addition of trastuzumab.[223] At 5-year follow-up, a comparison of the two arms (ie, chemotherapy with and without trastuzumab) demonstrated that the HRs for distant DFS (HR, 0.65; 95% CI, 0.38–1.12; *P* = .12) and OS (HR, 0.55; 95% CI, 0.27–1.11; *P* = .094) were higher relative to those reported at 3 years.[350]

All of the adjuvant trials of trastuzumab have demonstrated clinically significant improvements in DFS, and the combined analysis from the

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NSABP B31 and NCCTG N9831 trials, and the HERA trial, showed significant improvement in OS 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. The benefits of trastuzumab are independent of ER status.[226,227] In the FNCLCC-PACS-04 trial, 528 women with HER2-positive, node-positive breast cancer were randomly assigned to receive trastuzumab or observation *after* completion of adjuvant anthracycline-based chemotherapy with or without docetaxel.[358] No statistically significant DFS or OS benefit was observed with the addition of trastuzumab. These results suggest that the sequential administration of trastuzumab following chemotherapy is not as efficacious as a schedule involving concomitant chemotherapy and trastuzumab. The NCCN Guidelines recommend a total of 12 months of adjuvant trastuzumab as the standard of care. Shorter than 12-month duration has not been found to be as effective[359] and longer than 12 months duration does not have any added benefit, it has been found to be as effective as the 12 months of trastuzumab therapy.[360]

Retrospective analyses of low-risk patients with small tumors demonstrate that in T1a-bN0 breast cancers, HER2 overexpression added a 15% to 30% risk for recurrence.[361-364] These risks rates are substantially higher than seen among similarly sized HER2-negative tumors.

A recent single-arm, multicenter trial studied the benefit of trastuzumab-based chemotherapy in patients with HER2-positive, node-negative tumors less than or equal to 3 cm. All patients received trastuzumab and weekly paclitaxel for 12 weeks, followed by completion of a year of trastuzumab monotherapy.[365] Fifty percent of patients enrolled had tumors less than or equal to 1.0 cm and 9% of patients had tumors that were between 2 and 3 cm. The endpoint of the study was DFS. The results presented at the 2013 Annual San Antonio Breast Cancer Symposium demonstrated that the 3-year DFS rate in the overall population was 98.7% (95% CI, 97.6–99.8; $P < .0001$).

Dual anti-HER2 blockade associated with trastuzumab plus lapatinib and trastuzumab plus pertuzumab has shown significant improvements in the pCR rate when compared with chemotherapy associated with one anti-HER2 agent in the neoadjuvant setting.[366-368]

However, in the adjuvant setting, the results of the ALTTO trial failed to demonstrate a significant improvement in DFS with dual anti-HER2 therapy compared with trastuzumab alone.[369] After a median follow-up of 4.5 years, the DFS rates were 86% for patients who received trastuzumab alone; 88% for participants treated with trastuzumab and lapatinib concurrently; and 87% for patients who received trastuzumab followed by lapatinib.[369]

NCCN Recommendation for Adjuvant HER2-Targeted Therapy
Based on these studies, the panel has designated use of trastuzumab with chemotherapy as a category 1 recommendation in patients with HER2-positive tumors greater than 1 cm.

The NCCN Panel suggests trastuzumab and chemotherapy be used for women with HER2-positive, node-negative tumors measuring 0.6 to 1.0 cm (ie, T1b) and for smaller tumors that have less than or equal to 2 mm axillary node metastases (pN1mi). Some support for this recommendation comes from studies showing a higher risk of recurrence for patients with HER2-positive, node-negative tumors less than or equal to 1 cm compared to those with HER2-negative tumors of the same size.[361] 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 tumors, and

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70% and 61%, respectively, in women with HER2-positive, ER-negative tumors. Two more retrospective studies have also investigated recurrence-free survival in this patient population. None of the patients in these two retrospective studies received trastuzumab. In the first study, 5-year recurrence-free survival rates of 77.1% and 93.7% (P < .001) were observed for patients with HER2-positive and HER2-negative T1a-bN0M0 breast tumors, respectively, with no recurrence-free survival differences seen in the HER2-positive group when hormonal receptor status was considered.[362] In the other retrospective study of women with small HER2-positive tumors, the risk of recurrence at 5 years was low (99% [95% CI; 96%–100%] for HER2-negative disease and 92% [95% CI; 86%–99%] for HER2-positive disease).[370] Subgroup analyses from several of the randomized trials have shown consistent benefit of trastuzumab irrespective of tumor size or nodal status.[228,371,372]

NCCN Recommended HER-Targeted Regimens

The panel recommends AC followed by paclitaxel with trastuzumab for 1 year commencing with the first dose of paclitaxel as a preferred HER2 targeting adjuvant regimen. The TCH regimen is also a preferred regimen, especially for those with risk factors for cardiac toxicity, given the results of the BCIRG 006 study that demonstrated superior DFS in patients receiving TCH or AC followed by docetaxel plus trastuzumab compared with AC followed by docetaxel alone.

Other trastuzumab-containing regimens included in the NCCN Guidelines are: AC followed by docetaxel and trastuzumab,[228] and docetaxel plus trastuzumab followed by FEC[223] (see *Neoadjuvant/Adjuvant Chemotherapy* in the algorithm for a complete list of regimens).

Considering the unprecedented improvement in OS in the metastatic setting[373] and the significant improvement in pCR seen in the neoadjuvant setting,[367,368] the NCCN Panel considers it reasonable to incorporate pertuzumab into the above adjuvant regimens, if the patient did *not* receive pertuzumab as a part of neoadjuvant therapy. An ongoing study is evaluating pertuzumab and trastuzumab with standard chemotherapy regimens in the adjuvant setting.[374,375]

The NCCN Panel has included paclitaxel and trastuzumab as an option for patients with low-risk, HER2-positive, stage 1 tumors. This is based on a trial that studied this combination in 406 patients with small, node-negative, HER2-positive tumors. The results showed that the 3-year rate of disease-free survival was 98.7% (95% CI, 97.6–99.8) and the risk of serious toxic effects with this regimen was low (incidence of heart failure reported was 0.5%).[376]

Adjuvant Therapy for Tumors of Favorable Histologies

The guidelines provide systemic treatment recommendations for the favorable histology of invasive breast cancers, such as tubular and mucinous cancers, based on tumor size and ALN status. If used, the treatment options for endocrine therapy, chemotherapy, and sequencing of treatment with other modalities are similar to those of the usual histology of 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 reviewed if a tubular breast cancer is ER-negative and/or HER2-positive, or if a tumor with an ER- and PR-negative status is grade 1.[15] Should a breast cancer be histologically identified as a tubular or 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

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that prospective data regarding systemic adjuvant therapy of tubular and mucinous histologies are lacking.

Systemic Therapy for Triple-Negative Breast Cancer

For women with triple-negative breast cancer, several clinical trials sought to determine whether the addition of carboplatin (alone or in combination) as neoadjuvant chemotherapy can improve outcomes for women with triple-negative breast cancer. In the German GeparSixto trial, 315 patients with triple-negative breast cancer were administered neoadjuvant therapy consisting of weekly paclitaxel plus non-pegylated liposomal doxorubicin with bevacizumab and then randomly assigned to additional treatment with weekly carboplatin.[377] The addition of carboplatin achieved a pCR rate of 59% compared with pCR of 38% in patients who did not receive carboplatin.[377]

In the CALGB 40603 randomized phase II trial, 443 patients with stage II to III triple-negative breast cancer received standard anthracycline- and taxane-based chemotherapy with or without carboplatin and with or without bevacizumab. Compared with standard chemotherapy, the addition of carboplatin resulted in significantly higher pCR rate (54% vs. 41%, OR 1.71).[378] The addition of bevacizumab increased the numeric rate of pCR but was not statistically significant (with bevacizumab, pCR was 52% [95% CI; 45%–58%] and without bevacizumab pCR was 44% [95% CI; 38%–51%]; P = .057). In this study,[378] as well as in the GeparSixto study,[377] the addition of carboplatin and/or bevacizumab led to increased rates of adverse events. Neutropenia and thrombocytopenia were more common with carboplatin. Hypertension and postsurgical complications were more common with bevacizumab.

Even though the results of randomized trials show improvement in pCR rates when carboplatin is added to anthracycline- and taxane-based chemotherapy, the long-term outcomes such as OS or DFS associated with the incorporation of carboplatin are not yet known. Therefore, at this time, the NCCN Panel does not recommend addition of carboplatin to neoadjuvant standard chemotherapy for patients with triple-negative breast cancer outside a clinical trial setting.

Medullary Carcinoma

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 is 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 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.

Post-Therapy Surveillance and Follow-up

See page MS-43.

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Stage III Invasive Breast Cancer

Staging and Workup

The staging evaluation for most patients with stage III invasive breast cancer is similar to the one for patients with T3, N1, M0 disease. The workup includes history and physical exam, a CBC, liver function and alkaline phosphatase tests, chest imaging, pathology review, and pre-chemotherapy determination of tumor ER/PR receptor status and HER2 status. Diagnostic bilateral mammogram and breast ultrasound should be performed as clinically warranted. Genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer as defined by the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.

The performance of other studies, such as a breast MRI, a bone scan (category 2B), and abdominal imaging with diagnostic CT (with or without pelvic CT) or MRI (all category 2A) are optional unless directed by symptoms or other abnormal study results. PET/CT scan is also included as an optional additional study (category 2B). Ultrasound is an alternative when diagnostic CT or MRI is unavailable.

The consensus of the panel is that FDG PET/CT is most helpful in situations where standard imaging results are equivocal or suspicious. However, limited studies[101,102,379-383] support a potential role for FDG PET/CT to detect regional node involvement as well as distant metastases in locally advanced breast cancer, including T3, N1, M0 disease.

A retrospective study comparing bone scan with integrated FDG PET/CT, in women with stages I–III breast cancer with suspected metastasis, observed a high concordance (81%) between the two studies for reporting osseous metastases.[384] The NCCN Panel suggests that bone scan may be omitted if FDG PET/CT results are positive for bone metastases.

Equivocal or suspicious sites identified by PET/CT scanning should be biopsied for confirmation whenever possible and if the site of disease would impact the course of treatment. In the past decade, the advent of PET/CT scanners has significantly changed the approach to PET imaging.[385] However, the terminology has also created confusion regarding the nature of the scans obtained from a PET/CT device. PET/CT scanners have both a PET and CT scanner in the same gantry that allows precise coregistration of molecular (PET) and anatomic (CT) imaging. Almost all current clinical PET imaging is performed using combined PET/CT devices.

In PET/CT tomographs, the CT scanner has a second important role beyond diagnostic CT scanning.[385] For PET applications, the CT scan is also used for photon attenuation correction and for anatomic localization of the PET imaging findings. For these tasks, the CT scan is usually taken without breathholding, to match PET image acquisition, and typically uses low-dose (non-diagnostic) CT. Radiation exposure for these non-diagnostic CT scans is lower than for diagnostic CT. Intravenous contrast is not needed for this task.

PET/CT scanners typically include a high-quality CT device that can also be used for stand-alone, optimized, and fully diagnostic CT. Diagnostic CT scans are acquired using breathholding for optimal chest imaging, and are often performed with intravenous contrast. For fully diagnostic CT, the CT beam current, and therefore patient radiation exposure, is considerably higher than for the low-dose CT needed for PET requirements. Radiation exposures for fully diagnostic CT are often greater than for the emission (PET) component of the study.

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Currently, the approach to clinical PET/CT imaging varies widely across centers.[386] Many centers perform low-dose CT as part of a PET/CT scan, and perform optimized, fully diagnostic CT only when diagnostic CT has also been requested in addition to PET/CT. Other centers combine diagnostic CT scans with PET on all of their PET/CT images. The CT scans described in the workup section of the guidelines refer to fully optimized diagnostic CT scans, while the PET or PET/CT scans refer to scans primarily directed towards the PET component, not necessarily using diagnostic-quality CT. It is important for referring physicians to understand the differences between PET/CT performed primarily for PET imaging and fully optimized CT performed as a stand-alone diagnostic CT examination.[386] It may be convenient to perform PET/CT and diagnostic CT at the same time.

Operable Locally Advanced Breast Cancer

(Clinical stage T3, N1, M0)

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: 1) those where an initial surgical approach is unlikely to successfully remove all disease or to provide long-term local control; and 2) 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 T3, N1, M0 disease versus those who have clinical Tany, N2, M0 disease, based on evaluation by a multidisciplinary team.

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 T3, N1, M0], clinical stage IIIB, or clinical stage IIIC)

For patients with inoperable, non-inflammatory, locally advanced disease at presentation, the initial use of anthracycline-based preoperative systemic therapy with or without a taxane is standard therapy.[387] Patients with locally advanced breast cancer that is HER2-positive should receive an initial chemotherapy program that incorporates preoperative trastuzumab and possibly pertuzumab. Local therapy following a clinical response to preoperative systemic therapy usually consists of: 1) total mastectomy with level I/II ALN 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. Without detected internal mammary node involvement, consideration may be given to include the internal mammary lymph nodes in the radiation field (category 2B). Adjuvant therapy may involve completion of planned chemotherapy regimen course if not completed preoperatively, followed by endocrine therapy in patients with hormone receptor-positive disease. Up to one year of total trastuzumab therapy should be completed if the tumor is HER2-positive (category 1). Endocrine therapy and trastuzumab can be administered concurrently with radiation therapy if indicated.

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Patients with an inoperable stage III tumor with disease progression during preoperative systemic therapy 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 early-stage invasive breast cancer.

Post-Therapy Surveillance and Follow-up

Post-therapy follow-up is optimally performed by members of the treatment team and includes the performance of regular history/physical examinations every 4 to 6 months for the first 5 years after primary therapy and annually thereafter. Mammography should be performed annually.

The routine performance of alkaline phosphatase and liver function tests are not included in the guidelines.[388-390] 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.[101,391]

The use of dedicated breast MRI may be considered as an option for post-therapy surveillance and follow-up in women at high risk for bilateral disease, such as carriers of *BRCA1/2* mutations. Rates of contralateral breast cancer following either breast-conserving therapy or mastectomy have been reported to be increased in women with *BRCA1/2* mutations when compared with patients with sporadic breast cancer.[392-394] (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian and NCCN Guidelines for Breast Cancer Screening and Diagnosis).

The panel recommends that women with intact uteri who are taking adjuvant 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.[395] 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.

If an adjuvant 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.[313] 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.

Symptom management for women on adjuvant endocrine therapies often requires treatment of hot flashes and the treatment of concurrent depression. Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI) has been studied and is an effective intervention in decreasing hot flashes.[396-399] There is evidence suggesting that concomitant use of tamoxifen with certain SSRIs (eg, paroxetine, fluoxetine) may decrease plasma levels of endoxifen, an active metabolite of tamoxifen.[400,401] These SSRIs/SNRIs may interfere with the enzymatic conversion of tamoxifen to endoxifen by inhibiting a particular isoform of CYP2D6. However, the mild CYP2D6 inhibitors such as citalopram, escitalopram,

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sertraline, and venlafaxine appear to have no or only minimal effect on tamoxifen metabolism.[313,402,403]

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.[404] 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.

Lymphedema is a common complication after treatment for breast cancer. Factors associated with increased risk of lymphedema include extent of axillary surgery, axillary radiation, infection, and patient obesity.[405,406] The panel recommends educating the patients on lymphedema, monitoring for lymphedema, and referring for lymphedema management as needed.

Evidence suggests that a healthy lifestyle may lead to better breast cancer outcomes. A nested case control study of 369 women with ER-positive tumors who developed a second primary breast cancer compared with 734 matched control patients who did not develop a second primary tumor showed an association between obesity (body mass index [BMI] ≥30), smoking, and alcohol consumption and contralateral breast cancer.[407] A prospective study of 1490 women diagnosed with stage I–III breast cancer showed an association between high fruit and vegetable consumption, physical activity, and improved survivorship, regardless of obesity.[408] There is emerging evidence that obesity is associated with poorer outcomes for certain subtypes of breast cancers. The study by the Women's Intervention Nutrition group randomized early-stage breast cancer patients to an intervention group and a control group. The intervention consisted of eight one-on-one visits with a registered dietitian who had been trained on a low-fat eating plan. OS analysis showed no significant difference between the two study arms (17% for the intervention vs. 13.6% without); however, subgroup analysis showed that those with ER- and PR-negative disease who were part of the intervention group saw a 54% improvement in OS.[409] The NCCN Panel recommends an active lifestyle and ideal body weight (BMI 20–25) for optimal overall health and breast cancer outcomes.

Many young women treated for breast cancer maintain or regain premenopausal status following treatment for breast cancer. For these women, the NCCN Panel discourages the use of hormonal birth control methods, regardless of the hormone receptor status of the tumor.[410] Alternative birth control methods are recommended, including intrauterine devices, barrier methods, and, for those with no intent of future pregnancy, tubal ligation or vasectomy for the partner. Breastfeeding during endocrine or chemotherapy treatment is not recommended by the NCCN Panel because of risks to the infant. Breastfeeding after breast-conserving treatment for breast cancer is not contraindicated. However, lactation from an irradiated breast may not be possible, or may occur only with a diminished capacity.[410,411]

The panel recommends that women on an adjuvant 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. The use of estrogen, progesterone, or selective ER 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.

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Recent data show that adjuvant denosumab significantly reduces fractures in postmenopausal women receiving adjuvant therapy aromatase inhibitors, and improves bone mineral density.[412] Optimal duration of bisphosphonate therapy has not been established. Factors to consider for duration of anti-osteoporosis therapy include bone mineral density, response to therapy, and risk factors for continued bone loss or fracture. Women treated with a bisphosphonate should undergo a dental examination with preventive dentistry prior to the initiation of therapy, and should take supplemental calcium and vitamin D.

Stage IV Metastatic or Recurrent Breast Cancer

Staging and Workup

The staging evaluation of women who present with metastatic or recurrent breast cancer includes history and physical exam; the performance of a CBC, liver function tests, chest diagnostic CT, bone scan, and radiographs of any long or weight-bearing bones that are painful or appear abnormal on bone scan; consideration of diagnostic CT of the abdomen (with or without diagnostic CT of the pelvis) or MRI scan of the abdomen; and biopsy documentation of first recurrence if possible. The panel generally discourages the use of sodium fluoride 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**.** There is limited evidence (mostly from retrospective studies) to support the use of PET/CT scanning to guide treatment planning through determination of the extent of disease in select patients with recurrent or metastatic disease.[101,102,413,414] The panel considers biopsy of equivocal or suspicious sites to be more likely than PET/CT scanning to provide accurate staging information in this population of patients.

The consensus of the panel is that FDG PET/CT is optional (category 2B) and most helpful in situations where standard imaging results are equivocal or suspicious. The NCCN Panel recommends bone scan or sodium fluoride PET/CT to detect bone metastases (category 2B). However, if the FDG PET results clearly indicate bone metastasis, these scans can be omitted.

The NCCN Panel recommends that metastatic disease at presentation or first recurrence of disease should be biopsied as a part of the workup for patients with recurrent or stage IV disease. This ensures accurate determination of metastatic/recurrent disease and tumor histology, and allows for biomarker determination and selection of appropriate treatment.

Determination of hormone receptor status (ER and PR) and HER2 status should be repeated in all cases when diagnostic tissue is obtained. ER and PR assays may be falsely negative or falsely positive, and there may be discordance between the primary and metastatic tumors.[415,416] The reasons for the discordance may relate to change in biology of disease, differential effect of prior treatment on clonal subsets, tumor heterogeneity, or imperfect accuracy and reproducibility of assays.[416] Discordance between the receptor status of primary and recurrent disease has been reported in a number of studies. The discordance rates are in the range of 3.4% to 60% for ER-negative to ER-positive; 7.2% to 31% for ER-positive to ER-negative; and 0.7% to 11% for HER2.[417-426]

The NCCN Panel recommends that re-testing the receptor status of recurrent disease be performed, *especially* in cases when it was previously unknown, originally negative, or not overexpressed. For patients with clinical courses consistent with hormone receptor–positive breast cancer, or with prior positive hormone receptor results, the panel

has noted that a course of endocrine therapy is reasonable, regardless of whether the receptor assay is repeated or the result of the most recent hormone receptor assay.

Genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer, as defined by the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.

Management of Local Disease Only

Patients with local recurrence only are divided into 3 groups: those who had been treated initially by mastectomy alone, those who had been treated initially by mastectomy plus radiation therapy, and those who had received breast-conserving therapy.

In one retrospective study of local recurrence patterns in women with breast cancer who had undergone mastectomy and adjuvant chemotherapy without radiation therapy, the most common sites of local recurrence were at the chest wall and the supraclavicular lymph nodes.[427] The recommendations for treatment of the population of patients experiencing a local recurrence only are supported by analyses of a combined database of patients from the EORTC 10801 and Danish Breast Cancer Cooperative Group 82TM trials. The analyses compared breast-conserving therapy with mastectomy in patients with stage I and stage II disease. The 133 (approximately 8%) patients experiencing a local recurrence as an initial event were approximately equally divided between those who had undergone mastectomy and those who had received breast-conserving therapy as initial treatment for breast cancer. Of those in the former group, 51 (76%) were able to undergo radiation therapy with or without surgery as treatment for local disease recurrence. No difference in survival emerged between patients receiving treatment after initial treatment with mastectomy or breast-conserving therapy; approximately 50% of both groups were alive at 10-year follow-up.[428]

According to the NCCN Panel, 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 the chest wall and supraclavicular area (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 staging if a level I/II axillary dissection was not previously performed. Limited data suggest that a repeat SLN biopsy following local recurrence of disease may be successfully performed in 80% of women who have previously undergone breast-conserving therapy and sentinel node biopsy.[429] The consensus of the panel is that the preferred surgical approach for most women with a local recurrence following breast-conserving therapy and sentinel node biopsy is mastectomy and a level I/II axillary dissection, although sentinel node biopsy in lieu of a level I/II axillary dissection can be considered if prior axillary staging was done by sentinel node biopsy only.

The results of the CALOR trial found that after complete resection in patients with isolated locoregional recurrence, adjuvant chemotherapy improves both DFS and OS.[430] After median follow-up of 4.9 years, the overall DFS was 69% in the chemotherapy group versus 57% in the group that did not receive chemotherapy (HR = 0.59, P = .046).[430] Five-year OS in all patients in the study was also significantly improved with chemotherapy (88% vs. 76%, P = .024).[430] The benefit of adjuvant

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chemotherapy was mostly seen in women with ER-*negative* disease. Among women with ER-negative disease, 5-year DFS was 67% versus 35% (HR = 0.32, 95% CI = 0.14–0.73) and in those ER-positive disease, the 5-year DFS was 70% versus 69% (HR = 0.94, 95% CI = 0.47–1.89).[430]

According to the NCCN Panel, 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 panel emphasized the importance of individualizing treatment strategies in patients with a recurrence of disease limited to a local site.

Management of Stage IV or Recurrent Metastatic 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.[431]

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 bone metastasis is present. These two patient subsets are then stratified further by tumor hormone receptor and HER2 status.

Supportive Therapy for Bone Metastases

Treatment targeting osteoclast activity is of value in patients with metastatic breast cancer in bone to prevent bone fractures, bone pain requiring radiation therapy, spinal cord compression, and hypercalcemia (skeletal-related events; SREs).[432-434] The bisphosphonates zoledronic acid or pamidronate have been used for this purpose, and there is extensive clinical trial support for their efficacy in prevention of SREs (see section below on *Bisphosphonates*). Denosumab is a fully human monoclonal antibody directed against RANK ligand, a mediator of osteoclast function.[435] A single, randomized, active, controlled trial in metastatic breast cancer showed equivalency and superiority of time to the occurrence of SRE with denosumab, as compared with zoledronic acid.[434] No study of bisphosphonate or denosumab has demonstrated an impact on OS in patients with metastatic disease.

The bisphosphonates and denosumab are associated with a risk of development of osteonecrosis of the jaw (ONJ). Poor baseline dental health or dental procedures during treatment are known risk factors for ONJ. Thus, a dental examination with preventive dentistry intervention is recommended prior to treatment with intravenous bisphosphonate or denosumab, and dental procedures during treatment should be avoided if at all possible. Additional risk factors for the development of ONJ include administration of chemotherapy or corticosteroids and poor oral hygiene with periodontal disease and dental abscess.[436]

Confirmation of metastatic disease by imaging, including x-ray, diagnostic 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 or subcutaneous denosumab treatment in patients with metastatic disease. Frequent measurement of calcium, phosphorous, and magnesium may be prudent since hypophosphatemia and hypocalcemia have been reported.

Bisphosphonates

An intravenous bisphosphonate (eg, pamidronate, zoledronic acid) in combination with oral calcium citrate and vitamin D supplementation should be used in women with bone metastasis, especially if lytic and/or

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in weight-bearing bone, if expected survival is 3 months or longer, and if creatinine levels are below 3.0 mg/dL (category 1).[433,437-442] Bisphosphonates are given in addition to chemotherapy or endocrine therapy. Zoledronic acid may be superior to pamidronate in lytic breast metastasis.[443,444]

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 include the use of zoledronic acid and pamidronate in the United States and ibandronate and clodronate in European countries.[440,442,444-449] In metastatic bone disease, bisphosphonate treatment is associated with fewer skeletal-related events, fewer 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 OS has been observed in patients treated with bisphosphonates. The data indicate that zoledronic acid and pamidronate may be given on a 3- to 5-week schedule in conjunction with antineoplastic therapy (ie, endocrine therapy, chemotherapy, biologic therapy). Recent data from a phase III study showed zoledronic acid administered once every 12 weeks versus the current standard of once every four weeks does not compromise efficacy among women with breast cancer and bone metastases. The SRE rate was 22% when zoledronic was administered every 4 weeks versus 23.2% when administered once in 12 weeks.[450]

The use of bisphosphonates should be accompanied by calcium and vitamin D supplementation with daily doses of calcium of 1200 to 1500 mg and vitamin D_3 400 to 800 IU. Recommended agents for use in the United States are pamidronate 90 mg intravenously over 2 hours or zoledronic acid 4 mg 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.[447,449,451] 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 2 years. Longer durations of bisphosphonate therapy may provide additional benefit, but this has not yet been tested in clinical trials.

ONJ, a complication of bisphosphonate treatment, has been described. In a review of more than 16,000 cancer patients, an increased risk for 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.[452] It is recommended that patients should undergo a dental examination with preventive dentistry prior to initiation of bisphosphonate therapy.

Denosumab

Women with metastatic breast cancer to bone who are candidates for bisphosphonate therapy may also be considered for treatment with denosumab (category 1). This recommendation is based on the results of a single randomized trial comparing denosumab to zoledronic acid.[434] All trial patients were recommended to supplement with vitamin D and calcium. Patients on the experimental arm were given 120 mg of denosumab injected subcutaneously every 4 weeks plus intravenous placebo versus the control arm where patients were given an intravenous infusion of 4 mg of zoledronic acid every 4 weeks, and a subcutaneous placebo. In this trial with non-inferiority as the primary endpoint, denosumab was shown to significantly delay time to first SRE by 18% as compared with zoledronic acid (HR, 0.82; 95% CI, 0.71–

0.95; *P* < .001 for non-inferiority; *P* = .01 for superiority) and time to first and subsequent SREs (rate ratio, 0.77; 95% CI, 0.66–0.89; *P* = .001). No difference in time to progression or OS was observed. Adverse event profiles were similar for the two groups, including incidence of ONJ, with a reduced risk of renal-related and acute phase adverse events in the denosumab treatment group. Long-term risks of denosumab treatment are unknown. The optimal duration of treatment with denosumab is not known.

Endocrine Therapy for Stage IV or Recurrent Metastatic Disease

Women with recurrent or metastatic disease characterized by tumors that are ER- and/or PR-positive are appropriate candidates for initial endocrine therapy.

In premenopausal women, endocrine therapies include selective ER modulators (tamoxifen or toremifene); LHRH agonists (goserelin and leuprolide); surgical or radiotherapeutic oophorectomy; progestin (megestrol acetate); androgens (fluoxymesterone); and high-dose estrogen (ethinyl estradiol). For most premenopausal patients the use of ovarian suppression or ablation in combination with endocrine therapy for postmenopausal women is appropriate.

In premenopausal women without previous exposure to an antiestrogen, initial treatment is with selective ER modulator alone or ovarian suppression/ablation plus endocrine therapy as for postmenopausal women.[453] In premenopausal women with previous antiestrogen therapy who are within one year of antiestrogen exposure, the preferred second-line therapy is ovarian ablation or suppression followed by endocrine therapy as for postmenopausal women.

Endocrine therapies in postmenopausal women include nonsteroidal aromatase inhibitors (anastrozole and letrozole); steroidal aromatase inhibitors (exemestane); serum ER modulators (tamoxifen or toremifene); ER down-regulators (fulvestrant); progestin (megestrol acetate); androgens (fluoxymesterone); and high-dose estrogen (ethinyl estradiol) and recently several new combination therapies with novel agents have become available.

According to some studies, aromatase inhibitors appear to have superior outcome compared with tamoxifen, although the differences are modest.[454-457] A Cochrane review has also suggested a survival benefit favoring the aromatase inhibitors over other endocrine therapies, although the advantage is small.[458] A randomized phase III trial comparing tamoxifen with exemestane as first-line endocrine therapy for postmenopausal women with metastatic breast cancer showed no significant differences in progression-free survival (PFS) or OS between the two arms.[456]

Fulvestrant appears to be at least as effective as anastrozole in patients whose disease progressed on previous tamoxifen.[459,460] A randomized phase II study compared anastrozole versus fulvestrant in over 200 patients with advanced breast cancer.[461,462] In the initial analysis, fulvestrant was as effective as anastrozole in terms of overall response (36.0% vs. 35.5%; odds ratio, 1.02; 95% CI, 0.56 –1.87; *P* = .947) in evaluable patients (n = 89 for fulvestrant and n = 93 for anastrozole).[461] An improved time to progression was seen with fulvestrant compared to anastrazole (median time to progression was 23.4 months for fulvestrant vs. 13.1 months for anastrozole; HR, 0.63; 95% CI, 0.39–1.00; *P* =.0496).[462] This study used a higher 500 mg loading dose every 2 weeks for 3 doses and then 500 mg monthly.[461] The median OS was longer in the fulvestrant group than in the anastrozole group (54.1 months vs. 48.4 months; HR, 0.70; *P* = .041). [463]

A phase II study of fulvestrant in postmenopausal women with advanced breast cancer and disease progression following aromatase

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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.[464] 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* = .853).[465] In that study, fulvestrant was administered as a 500 mg loading dose followed by doses of 250 mg on day 14, day 28, and then monthly.

A separate phase III randomized study in postmenopausal women with metastatic ER-positive breast cancer compared fulvestrant 500 mg every 2 weeks for 3 doses followed by 500 mg monthly versus fulvestrant 250 mg monthly. The PFS was superior with the fulvestrant 500 mg regimen (HR 0.80; 95% CI, 0.68–0.94; *P* = .006),[466] indicating an increased duration of response with the higher dose of fulvestrant. The final analyses demonstrated an increase in median OS (4.1 months) and reduced risk of death (19%) with a dose of 500 mg compared with 250 mg. Median OS was 26.4 versus 22.3 months (HR, 0.81; 95% CI, 0.69–0.96; *P* = .02).[467]

Combination endocrine therapy in postmenopausal women with hormone receptor-positive, previously *untreated* metastatic breast cancer has been reported from two studies comparing single-agent anastrozole versus anastrozole plus fulvestrant.

In one study (FACT), combination endocrine therapy was not superior to single-agent anastrozole (time to progression HR, 0.99; 95% CI, 0.81–1.20; *P* = .91).[468] In the second study (S0226), PFS (HR, 0.80; 95% CI, 0.68–0.94; stratified log-rank *P* = .007) and OS (HR, 0.81; 95% CI, 0.65–1.00; stratified *P* = .049) were superior with combination anastrozole plus fulvestrant.[469] An unplanned subset analysis in this trial suggested that patients without prior adjuvant tamoxifen experienced the greatest benefit. The reason for the divergent outcomes in these two studies is not known.

A phase III trial studied the effect of fulvestrant alone or in combination with anastrozole or exemestane in patients with advanced breast cancer and an acquired non-steroidal aromatase inhibitor-resistant disease.[470] An aromatase inhibitor had been given as adjuvant treatment to 18% of patients for a median of 27.9 months, and to 82% of patients for locally advanced/metastatic disease for a median of 19.3 months. Median PFS was 4.8 months, 4.4 months, and 3.4 months for patients treated with fulvestrant alone, anastrazole plus fulvestrant, and fulvestrant plus exemestane, respectively. No differences were observed for overall response rate, clinical benefit rate, and OS. This trial provides no evidence that adding an aromatase inhibitor to fulvestrant in patients with non-steroidal aromatase inhibitor-resistant disease improves the results achieved with fulvestrant alone. In postmenopausal women who have received previous antiestrogen therapy and are within one year of antiestrogen exposure, there is evidence supporting the use of a selective aromatase inhibitor as the preferred first-line therapy for their recurrent disease.[471,472]

New agents, such as palbociclib, a highly selective inhibitor of CDK 4/6 kinase activity, now have a role in treating women with ER-positive metastatic breast cancer in combination with endocrine therapy. A phase 2, open-label, randomized, multicenter trial evaluated the safety and efficacy of palbociclib in combination with letrozole versus letrozole alone as first-line treatment for patients with advanced ER-positive, HER2- breast cancer.[473] Median PFS reported was double with the combination regimen compared to letrozole alone (20.2 months for the palbociclib plus letrozole group and 10.2 months for the letrozole alone group; HR, 0.488; 95% CI, 0.319–0.748).[473] The grade 3/4 adverse

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reactions reported at a higher incidence in the palbociclib plus letrozole versus letrozole alone included neutropenia (54% vs. 1%) and leukopenia (19% vs. 0%). Based on this study, the FDA approved palbociclib in combination with letrozole for the treatment of postmenopausal women with ER-positive, HER2- advanced breast cancer as initial endocrine-based therapy for their metastatic disease. The NCCN Panel has included the combination of palbociclib with letrozole as a first-line endocrine therapy option for postmenopausal patients with ER-positive, HER-negative metastatic breast cancer.

Limited studies document a PFS advantage of adding trastuzumab or lapatinib to aromatase inhibition in postmenopausal women with hormone receptor-positive metastatic breast cancer that is HER2-positive.[474,475]

Resistance to endocrine therapy in women with hormone receptor-positive disease is frequent. One mechanism of resistance to endocrine therapy is activation of the mammalian target of rapamycin (mTOR) signal transduction pathway. Several randomized studies have investigated the use of aromatase inhibition in combination with inhibitors of the mTOR pathway.

A randomized phase II study estimated the efficacy of tamoxifen alone versus tamoxifen combined with everolimus, an oral inhibitor of mTOR, in women with hormone receptor-positive, HER2-negative metastatic breast cancer previously treated with an aromatase inhibitor.[476] After a median follow-up of 13 months, an intent-to-treat analysis showed that the clinical benefit was 42.1% (95% CI, 29.1–55.9) with tamoxifen alone and 61.1% (95% CI, 46.9–74.1) with tamoxifen plus everolimus. An improvement in median time to progression was seen when everolimus was combined with tamoxifen compared with tamoxifen alone. Median time to progression was 4.5 months (95% CI, 3.7–8.7) with tamoxifen alone versus 8.5 months (95% CI, 6.01–13.9) with everolimus and tamoxifen.[476]

A phase III trial in postmenopausal women with advanced, hormone receptor-positive breast cancer with no prior endocrine therapy for advanced disease, randomized subjects to letrozole with or without the mTOR inhibitor temsirolimus has been reported.[477] In this study, PFS was not different between the treatment arms (HR, 0.89; 95% CI, 0.75–1.05; long-rank P = .18).

The results of this trial differ from that of the BOLERO-2 trial (described below). The reasons for the differences in the outcomes of these two randomized phase III studies[477,478] is uncertain, but may be related to the issues of patient selection and extent of prior endocrine therapy.

A phase III study (BOLERO-2) randomized postmenopausal women with hormone receptor-positive advanced breast cancer that had progressed or recurred during treatment with a nonsteroidal aromatase inhibitor to exemestane with or without the mTOR inhibitor everolimus.[479] Final results reported after median 18-month follow-up show that median PFS (by central review) remained significantly longer with everolimus plus exemestane versus placebo plus exemestane at 11.0 versus 4.1 months, respectively; (HR, 0.38; 95% CI, 0.31-0.48; P < .0001).[478] The adverse events (all grades) that occurred more frequently in those receiving everolimus included stomatitis, infections, rash, pneumonitis, and hyperglycemia.[478,479] Analysis of safety and efficacy in the elderly patients enrolled in this trial showed that elderly patients treated with an everolimus-containing regimen had similar incidences of these adverse events, but the younger patients had more on-treatment deaths.[480] The NCCN Panel agrees that the evidence from the BOLERO-2 trial is compelling enough to consider the addition of

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everolimus to exemestane in women who fulfill the entry criteria for BOLERO-2.

Many premenopausal and postmenopausal women with hormone-responsive breast cancer benefit from sequential use of endocrine therapies at 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 disease progression. After second-line endocrine therapy, little high-level evidence exists to assist in selecting the optimal sequence of endocrine therapy. Additional endocrine therapies for second-line and subsequent therapy are listed in the algorithms.

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.[481-483] Endocrine therapy is 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. Therefore, the NCCN Breast Cancer Panel recommends consideration of a trial of endocrine therapy for patients with disease characterized as hormone receptor-negative with disease localized to the bone or soft tissue only or with asymptomatic visceral disease, irrespective of HER2 tumor status.

Cytotoxic Chemotherapy for Stage IV or Recurrent Metastatic Disease

Women with hormone receptor-negative tumors not localized to the bone or soft tissue only, that are associated with symptomatic visceral metastasis, or that have hormone receptor-positive tumors that are refractory to endocrine therapy should receive chemotherapy. A variety of chemotherapy regimens are felt to be appropriate, as outlined in the treatment algorithm. 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.[484-488] 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 PFS can be prolonged with the use of continuous chemotherapy versus shorter-course chemotherapy.[489,490] Due to the lack of consistent OS differences, the use of prolonged versus shorter chemotherapy needs to be weighed against the detrimental effects of continuous chemotherapy on overall quality of life.

Single cytotoxic agents and combination chemotherapy regimens recommended by the panel for the treatment of patients with metastatic disease are listed in the NCCN Guidelines.

Single Agents

Single agents are categorized as either preferred or other single agents based on a balance of the efficacy, toxicity, and treatment schedules of the drugs. Among preferred 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, eribulin and vinorelbine.

Eribulin is a non-taxane microtubule inhibitor used for the treatment of patients with metastatic breast cancer who have previously received at

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least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting. In a phase III trial, 762 patients with metastatic breast cancer were randomized 2:1 to eribulin or treatment of physicians' choice. One-year OS was 53.9% for patients receiving eribulin versus 43.7% for the control arm, and median OS was 13.12 versus 10.65 months, representing a 19% statistically significant risk reduction (*P* = .041). Time to progression was greater with eribulin 3.7 versus 2.2 months for patients in the control arm (*P* = .14).[491]

Several studies have demonstrated that eribulin is active in metastatic breast cancer. A large randomized trial of heavily pre-treated patients with metastatic breast cancer compared treatment with eribulin versus therapy of physician's choice. Eribulin demonstrated significant improvement in OS with 2.5-month prolongation of median OS (median OS for patients treated with eribulin was 13.1 months compared with 10.6 months for those receiving other treatments. HR, 0.81; 95% CI, 0.66–0.99; *P* = .041).[491]

A phase III trial compared eribulin with capecitabine in patients with metastatic breast cancer. While a small survival advantage was observed with eribulin treatment in all subgroups of patients, there was a significant survival advantage observed with eribulin over capecitabine among patients with triple-negative breast cancer (15.9 vs. 13.5 months; HR, 0.838; 95% CI, 0.715–0.983; *P* =.030).[492]

Among other single agents, the panel includes: cyclophosphamide, carboplatin, docetaxel, albumin-bound paclitaxel, cisplatin, ixabepilone, and epirubicin.

Ixabepilone, an epothilone B analogue, is also used for treatment of recurrent or metastatic breast cancer as a single agent. 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 [493]; in patients with taxane-resistant metastatic breast cancer[494]; and in patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine.[495] In the phase II trials, objective response rate, median duration of response, and median OS duration were 41.5% (95% CI, 29.4%–54.4%), 8.2 months (95% CI, 5.7–10.2 months), and 22.0 months (95% CI, 15.6–27.0 months) in the first-line setting;[493] 12% (95% CI, 4.7%– 26.5%), 10.4 months, and 7.9 months for the taxane-resistant patients;[494] and 11.5% (95% CI, 6.3%–18.9%), 5.7 months, and 8.6 months for the patients previously treated with an anthracycline, a taxane, and capecitabine.[495] In the study by Perez et al,[495] grade 3/4 treatment-related toxicities included peripheral sensory neuropathy (14%) and neutropenia (54%).

Combination Regimens

Among combination regimens, the panel includes FAC/CAF; FEC; AC; EC; CMF; docetaxel, capecitabine; gemcitabine, paclitaxel; gemcitabine, carboplatin; and paclitaxel, bevacizumab.

A series of trials have sought to define the role for bevacizumab, a humanized monoclonal antibody against the vascular endothelial growth factor in the treatment of metastatic breast cancer. The E2100 trial randomized 722 women with recurrent or metastatic breast cancer to first-line chemotherapy with paclitaxel with or without bevacizumab.[496] This trial documented superior PFS (11.8 months vs. 5.9 months; HR 0.60; *P* <.001) favoring bevacizumab plus paclitaxel compared with paclitaxel alone. A similar trial enrolled 736 patients who were randomized to treatment with docetaxel and bevacizumab or docetaxel

and placebo.[497] This trial also documented increased PFS in the arm containing bevacizumab (10.1 months vs. 8.2 months with docetaxel alone; HR 0.77; *P* = .006). An additional trial, RIBBON-1, combined bevacizumab with capecitabine, with a taxane (docetaxel, nab-paclitaxel), with anthracyclines (FEC, CAF, AC, or EC), or with the same chemotherapy alone. Results of this trial show a statistically significant increase in PFS with bevacizumab and capecitabine (8.6 months vs. 5.7 months; HR, 0.69; *P* < .001) and taxane- or anthracycline- (9.2 months vs. 8.0 months; HR, 0.64; *P* < .001) containing arms.[498,499] None of these studies demonstrates an increase in OS or quality of life when analyzed alone or in a meta-analysis combining the trials.[500] The increase in PFS with bevacizumab is modest, and appears the greatest in combination with paclitaxel, especially as reported in an unpublished analysis provided to the FDA.[501]

As with endocrine therapy, sequential responses are often observed with chemotherapy, supporting the use of sequential single agents and combination chemotherapy regimens. The current guidelines include doses and schedules of these single agents and combination regimens for metastatic breast cancer. Failure to achieve a tumor response to 3 sequential chemotherapy regimens or 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 many anatomically localized problems that may benefit from local irradiation, surgery, or regional chemotherapy (eg, intrathecal methotrexate for leptomeningeal carcinomatosis).

HER2-Targeted Therapy for Stage IV or Recurrent Metastatic Disease

Patients with tumors that are HER2-positive may derive benefit from treatment with HER2-targeted therapy. The panel recommends selecting patients for HER2-targeted therapy if their tumors are either positive for HER2 by ISH or 3+ by IHC. HER2 testing recommendations are described in the guideline. Patients with tumors IHC 0 or 1+ for HER2 or ISH not amplified have very low rates of HER2-targeted response and HER2-targeted therapy.[502] Adequate standardization and validation of HER2 assays by ISH and IHC used in clinical practice is a concern, and data suggest that false-positive determinations are common.[20,21,503-505] Recommendations regarding HER2 testing have been published.[503,505]

First-Line Regimens for HER2-Positive Tumors

The NCCN Panel has categorized HER2-targeting regimens as either preferred or other.

Preferred First-Line Regimens

A randomized, double-blind, phase III study compared the efficacy and safety of pertuzumab in combination with trastuzumab and docetaxel versus trastuzumab and docetaxel as first-line treatment for HER2-positive metastatic breast cancer.[506] The primary endpoint of the study was independent assessment of PFS. The secondary endpoints were PFS assessed by investigator, objective response rate, OS, and safety. A total of 808 patients were enrolled in this trial.[506] The addition of pertuzumab provided a statistically significant improvement in PFS compared to trastuzumab plus docetaxel alone. The median independently assessed PFS was increased by 6.1 months, from 12.4 months in the control group to 18.5 months in the pertuzumab group (HR for progression or death, 0.62; 95% CI, 0.51– 0.75; *P* < .001).[506] At a median follow-up of 30 months the results showed a statistically significant improvement in OS in favor of the pertuzumab-containing

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regimen, with a 34% reduction in the risk of death (HR, 0.66; 95% CI, 0.52–0.84; *P* = .0008). The median OS was 37.6 months in the non-pertuzumab group and had not yet been reached in the pertuzumab-containing regimen.[373] The most common adverse reactions reported in the pertuzumab group compared to the control group were diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin. Peripheral edema and constipation were greater in the control group.[506] Cardiac adverse events or left ventricular systolic dysfunction were reported slightly more frequently in the control group.[507] Health-related quality of life was not different in the two treatment groups.[508]

Phase II trials have also found activity and tolerability for pertuzumab, pertuzumab with trastuzumab, and for other regimens combining pertuzumab and trastuzumab together with other active cytotoxics (ie, paclitaxel, vinorelbine).[509,510,511] Phase III trials of pertuzumab plus chemotherapy without trastuzumab have not been reported.

The NCCN Panel recommends pertuzumab plus trastuzumab in combination with a taxane as a preferred option for first-line treatment of patients with HER2-positive metastatic breast cancer. Pertuzumab plus trastuzumab in combination with docetaxel is an NCCN category 1 and in combination with paclitaxel is an NCCN category 2A recommendation.

Other First-Line Regimens for HER2-Positive Tumors

First-line trastuzumab in combination with selected chemotherapeutics[230] or as a single agent[229,231] is another option for HER2-positive metastatic breast cancer patients. Randomized trials demonstrate benefit from adding trastuzumab to other agents including paclitaxel with or without carboplatin,[230,502,512,513] docetaxel,[512] and vinorelbine,[512] or as a single agent[231] 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.[514,515] For those patients with hormone receptor-positive, HER2-positive disease, the panel recommends initial treatment with endocrine therapy, an approach consistent with most of these studies. 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.[230,515,516]

The NCCN Panel has listed trastuzumab with the following agents: paclitaxel alone or along with carboplatin; docetaxel; vinorelbine; and capecitabine as other first-line regimens for patients with HER2-positive systemic disease.

Regimens for Trastuzumab-Exposed HER2-Positive Disease

The NCCN Panel recommends continuation of HER2 blockade for patients with HER2-positive metastatic breast cancer that progresses on first-line trastuzumab-containing regimens. This recommendation also applies to the new class of patients who are diagnosed with HER2-positive metastatic disease following prior exposure to trastuzumab in the adjuvant setting. Several trials have demonstrated benefit of continuation of trastuzumab therapy following disease progression on a trastuzumab-containing regimen.[517-519] However, the optimal duration of trastuzumab in patients with long-term control of disease is unknown.

The NCCN Guidelines include doses and schedules of representative regimens for use in HER2-positive metastatic breast cancer.

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Preferred Regimen for Trastuzumab-Exposed HER-Positive Disease

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate. Through a stable linker, the HER2-targeting antitumor property of trastuzumab is conjugated with the cytotoxic activity of the microtubule-inhibitory agent DM1 (derivative of maytansine). A recent randomized, international, multicenter, open-label, phase III study (EMILIA) evaluated the safety and efficacy of T-DM1 compared with lapatinib plus capecitabine for HER2-positive patients with locally advanced breast cancer or metastatic breast cancer.[520] The primary endpoints of this study were PFS, OS, and safety. T-DM1 demonstrated a statistically significant improvement in both primary endpoints of PFS and OS.

PFS (assessed by independent review) was significantly improved with T-DM1 with median PFS of 9.6 months vs. 6.4 months with lapatinib plus capecitabine; HR for progression or death from any cause was 0.65 (95% CI, 0.55–0.77; $P < .001$). At the first interim analysis, T-DM1 also demonstrated significant improvement in OS. The stratified HR for death from any cause with T-DM1 versus lapatinib plus capecitabine was 0.62 (95% CI, 0.48–0.81; $P = .0005$).[520] Rates of grade 3 or 4 adverse events were higher with lapatinib plus capecitabine than with T-DM1 (57% vs. 41%). The incidences of thrombocytopenia and increased serum aminotransferase levels were higher with T-DM1 (frequency >25%), whereas the incidences of diarrhea, nausea, vomiting, and palmar-plantar erythrodysesthesia were higher with lapatinib plus capecitabine.[520]

The NCCN Panel recommends T-DM1 as a *preferred* option for treatment of patients with HER2-positive metastatic breast cancer who have previously received a trastuzumab-based regimen.

Other Regimens for Trastuzumab-Exposed HER2-Positive Disease

Pertuzumab is active in patients beyond the first-line setting. The results of a multicenter, open-label, single-arm, phase II study (n = 66) show that the combination of pertuzumab and trastuzumab is active and well tolerated in patients with HER2-positive metastatic breast cancer that has progressed on prior trastuzumab therapy. The trial reported an objective response rate of 24.2% and a clinical benefit rate of 50%.[521]

To determine whether the clinical benefit seen in the study was from pertuzumab alone or was a result of the combined effect of pertuzumab and trastuzumab, a cohort of patients (n = 29) whose disease progressed during prior trastuzumab-based therapy received pertuzumab monotherapy until progressive disease or unacceptable toxicity. Of these, patients with disease progression (n = 17) continued to receive pertuzumab with the addition of trastuzumab. In the 29 patients who received pertuzumab monotherapy, the objective response rate and clinical benefit rate reported were 3.4% and 10.3%, respectively, whereas in the patients who received dual blockade after progression on pertuzumab, the objective response rate and clinical benefit rate were 17.6% and 41.2%, respectively.[522]

According to the NCCN Panel, for patients with disease progression after treatment with trastuzumab-based therapy without pertuzumab, a line of therapy containing both trastuzumab plus pertuzumab with or without a cytotoxic agent (such as vinorelbine or taxane) may be considered. Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.

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.[523] 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; HR, 0.49; 95% CI, 0.34–0.71; *P* < .001). The patients who progressed on monotherapy were allowed to cross over to the combination arm. This resulted in insufficient power to detect significant differences in OS; an exploratory analysis demonstrated a trend toward a survival advantage with lapatinib plus capecitabine.[524] The analysis reported a median OS of 75.0 weeks for the combination arm and 64.7 weeks for the monotherapy arm (HR, 0.87; 95% CI, 0.71–1.08; *P* = .210).[524]

Another study of women with metastatic breast cancer showed that lapatinib in combination with letrozole increased PFS over letrozole alone in the subset of women with HER2-positive cancer (3.0 months for letrozole and placebo vs. 8.2 months for letrozole and lapatinib; HR, 0.71; 95% CI, 0.53–0.96; *P* = .019).[474] 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 PFS was increased from 8.1 weeks to 12 weeks (*P* = .008) with the combination.[525] The OS analysis data showed that lapatinib plus trastuzumab improved median survival by 4.5 months, with median OS of 14 months for the combination therapy and 9.5 months for lapatinib alone (HR, 0.74; 95% CI, 0.57–0.97; *P* = .026). [526] This improvement in OS analysis included patients who were initially assigned to monotherapy and crossed over to receive combination therapy at the time of progression.[526]

Based on the absence of data, the panel does not recommend the addition of chemotherapy to the trastuzumab and lapatinib combination.

Surgery for Stage IV or Recurrent Metastatic Disease

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.[527] 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.

Retrospective studies suggest a potential survival benefit from complete excision of the in-breast tumor in select patients with metastatic breast cancer.[528-531] Substantial selection biases exist in all of these studies and are likely to confound the study results.[532,533] Two recent prospective, randomized studies assessed whether or not surgery on the primary tumor in the breast is necessary for women who are diagnosed with metastatic/stage IV breast cancer. The results from both studies presented at the 2013 Annual San Antonio Breast Cancer Symposium were similar showing that surgical treatment of primary tumors in women presenting with stage IV disease does not produce an increase in OS.[534,535]

Nevertheless, the panel recognizes the need for randomized clinical trials that will address the risks and benefits of local therapy for patients

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with stage IV disease while eliminating selection biases. Patient enrollment in such trials is encouraged.

Distant Sites of Recurrence Requiring Consideration of Therapies Local to the Metastatic Site

Surgery, radiation, or regional chemotherapy (eg, intrathecal methotrexate) may be indicated as needed for localized clinical scenarios such as brain metastases, leptomeningeal disease, choroid metastases, pleural effusion, pericardial effusion, biliary obstruction, ureteral obstruction, impending pathologic fracture, cord compression, localized painful bone, or soft-tissue disease.

The guidelines include consideration of the addition of hyperthermia to irradiation for localized recurrences/metastasis (category 3). 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.[536,537] While there is heterogeneity among the study results, a 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.[536] No differences in OS 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.

Monitoring Metastatic Disease

Monitoring the treatment of metastatic breast cancer involves a wide array of assessments and the need for the clinician to integrate several different forms of information to make a determination of the effectiveness of treatment and the acceptability of toxicity. The information includes those from direct observations of the patient, including patient reported symptoms, performance status, change in weight, and physical examination; laboratory tests such as alkaline phosphatase, liver function, blood counts, and calcium; radiographic imaging; functional imaging; and, where appropriate, tumor biomarkers. The results of these evaluations generally are classified as response, continued response to treatment, stable disease, uncertainty regarding disease status, or progression of disease. The clinician typically must assess and balance multiple different forms of information to make a determination regarding whether disease is being controlled and the toxicity of treatment is acceptable. Sometimes this information may be contradictory.

The panel recommends using widely accepted criteria for reporting response, stability, and progression of disease such as the RECIST criteria[538] and the WHO criteria.[539] The NCCN Panel also recommends using the same method of assessment over time. For example, an abnormality initially found on diagnostic CT scan of the chest should be monitored with repeat diagnostic CT scans of the chest.

The optimal frequency of testing is uncertain, and is primarily based on the monitoring strategies utilized in breast cancer clinical trials. The page titled *Principles of Monitoring Metastatic Disease* in the algorithm provides a table outlining general recommendations for the frequency and type of monitoring as a baseline before initiation of new therapy, for monitoring the effectiveness of cytotoxic chemotherapy and endocrine

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therapy, and as an assessment when there is evidence of disease progression. The panel has indicated in a footnote that the frequency of monitoring can be reduced in patients who have long-term stable disease. These are guidelines and should be modified for the individual patient using clinical judgment, especially for those with stable or responding disease for long periods of time.

The clinical use of Circulating Tumor Cells (CTC) in metastatic breast cancer is not yet included in algorithms for disease assessment and monitoring. Patients with persistently increased CTC after 3 weeks of first-line chemotherapy have a poor PFS and OS.[540] In spite of its prognostic ability, CTC count has failed to show a predictive value. A prospective, randomized, phase 3 trial (SWOG S0500) evaluated the clinical utility of serial enumeration of CTC in patients with metastatic breast cancer. [540] According to the study results, switching to an alternative cytotoxic therapy after 3 weeks of first-line chemotherapy in patients with persistently increased CTC did not affect either PFS or OS.[540]

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 NAC.[541] 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% to 90% of cases.[542-544] The associated cancers are not necessarily located adjacent to the NAC 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. Any breast lesion identified by imaging or examination should be evaluated according to the NCCN Guidelines for Breast Screening and Diagnosis. The skin of the NAC should undergo surgical biopsy, including the full thickness of the epidermis including at least a portion of any clinically involved NAC. When biopsy of the NAC is positive for Paget's disease, breast MRI is recommended to define the extent of disease and identify additional disease.[544,545]

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.[543] 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 NAC followed by whole breast radiation therapy.[546-550] The risk of ipsilateral breast recurrence after breast-conserving NAC 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 NAC with a negative margin of underlying breast tissue. In cases with an associated cancer elsewhere

in the breast, the surgery includes removal of the NAC 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 NAC and the peripheral cancer in continuity in a single surgical specimen or through a single incision. Mastectomy also remains an appropriate treatment option.

ALN staging is not necessary when breast-conserving therapy is used to treat Paget's disease with underlying DCIS without evidence of invasive cancer following clinical examination, imaging evaluation, and full-thickness skin biopsy of the involved NAC. 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* outlined in the NCCN Guidelines. 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. This is because the final pathology may reveal an invasive cancer in the mastectomy specimen and the mastectomy precludes subsequent sentinel node biopsy. Two 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.[551,552] 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 the initial sections of the NCCN Guidelines. A radiation boost should be considered for the site of the resected NAC 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 ER-positive 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.

Phyllodes Tumors of the Breast

(also known as phyllodes tumors, cystosarcoma phyllodes)

Phyllodes tumors of the breast are rare tumors comprised of both stromal and epithelial elements.[553] 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.[554] The 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 of 40.[555] Phyllodes tumors often enlarge rapidly and are usually painless. Phyllodes tumors often appear on ultrasound and mammography as fibroadenomas, and FNA cytology and even core needle biopsy are inadequate to reliably distinguish phyllodes tumors from fibroadenoma.[555] 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 Li-Fraumeni syndrome (germline *TP53* mutation, see NCCN Guidelines for Genetic/Familial High Risk Assessment) have an increased risk for phyllodes tumors.[556] 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.

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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.[557] Since phyllodes tumors rarely metastasize to the ALNs, surgical axillary staging or ALN dissection is not necessary unless the lymph nodes are pathologic on clinical examination.[558] In those patients who experience a local recurrence, resection of the recurrence with wide, tumor-free surgical margins should be performed. Some panel members recommend local radiation therapy of the remaining breast or chest wall following resection of a local recurrence, but this recommendation is controversial (category 2B).[559]

While the epithelial component of most phyllodes tumors contains ER (58%) and/or PR (75%),[560] 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 Guidelines for Soft Tissue Sarcoma.

Breast Cancer During Pregnancy

Breast cancer occurring concurrently with pregnancy is an infrequent clinical event. In a California registry study, there were 1.3 breast cancers diagnosed per 10,000 live births.[561] Unfortunately, breast cancer during pregnancy is most often ALN-positive and with larger primary tumor size. Histologically the tumors are poorly differentiated, are more frequently ER/PR-negative, and approximately 30% are HER2-positive.[562,563] 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%.[564] 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.[564] Biopsies for cytologic evaluation of a suspicious breast mass may be done with 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 adequate tissue for hormone receptor and HER2 analyses.

Staging assessment of the pregnant patient with breast cancer may be guided by clinical disease stage. The staging studies should be tailored to minimize fetal exposure to radiation. For clinically node-negative T1-T2 tumors, a chest x-ray (with shielding), liver function and renal function assessment, and a CBC 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

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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, breast-conserving surgery is possible if radiation therapy can be delayed to the postpartum period,[565] and breast-conserving therapy during pregnancy does not appear to have a negative impact on survival.[565,566] When surgery is performed at 25 weeks of gestation or later, obstetrical and prenatal specialists must be onsite 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 SLN biopsy in pregnant patients,[567,568] 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 pregnant woman. Decisions related to use of SLN biopsy in pregnancy should be individualized. A 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.[569] There are limited data with only case reports and estimations of fetal radiation dose regarding use of radioactive tracer (eg, technetium 99m sulfur colloid).[570-572] Isosulfan blue or methylene blue dye for sentinel node biopsy procedures is discouraged 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 largest experience in pregnancy has been with anthracycline and alkylating agent chemotherapy.[573,574] Collected data of chemotherapy exposure in utero indicate that the first trimester has the greatest risk of fetal malformation.[575,576] 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 during delivery. Data from a single-institution prospective study indicate that FAC chemotherapy (5-FU 500 mg/m^2 IV days 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.[574] As reported by Gwyn et al, the median gestational age at delivery was 38 weeks, more than 50% of the patients had a vaginal delivery, and there were no fetal deaths.[562] 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 one child with Down's syndrome and two with congenital abnormalities (club foot; congenital bilateral ureteral reflux). The children are reported to be healthy and progressing well in school.[574,577] 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.[578-581] If used, the NCCN Panel recommends weekly administration of paclitaxel after the first trimester if clinically indicated by disease status. There are only case reports of trastuzumab use during pregnancy.[582-589] The majority 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

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postpartum period; the panel recommends against its use during pregnancy.

A single case report of first trimester exposure to lapatinib during treatment for breast cancer reported an uncomplicated delivery of a healthy female neonate.[590]

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

Communication between the oncologist and maternal fetal medicine specialist is essential at every visit and for every treatment decision point for the patient.

Inflammatory Breast Cancer

Inflammatory breast cancer (IBC) is a rare, aggressive form of breast cancer estimated to account for 1% to 6% of breast cancer cases in the United States.[591,592] 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.

IBC is usually hormone receptor-negative and is more frequently HER2-positive than the usual ductal breast cancers. Studies on gene expression profiling of IBC have demonstrated that all the subtypes of IBC exist, but basal and HER2 overexpressed are more frequent.[593-596] According to the 7th edition of the AJCC Cancer Staging Manual, IBC is classified 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 are 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 on clinical findings, and dermal lymphatic involvement is neither required, nor sufficient by itself, to assign a diagnosis of IBC.[26,597] 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 noninflammatory forms of locally advanced breast cancer, are more likely to have a less favorable prognosis[598-600] and to be younger at the time of disease presentation.[601]

The NCCN 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.[602,603] Nevertheless, current evidence provides justification for a separate guideline for the workup and treatment of patients diagnosed with IBC.

StageT4d, N0- N3, M0

Workup

Women with a clinical/pathologic diagnosis of IBC without distant metastasis (stage T4d, N0-N3, M0) should undergo a thorough staging evaluation by a multidisciplinary team.

Recommendations for workup include a complete history and physical examination involving a CBC and platelet count.

A pathology review and pre-chemotherapy determinations of tumor hormone receptor and HER2 receptor status should be performed.

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HER2 has a predictive role in determining which patients with IBC will benefit from HER2-targeted therapy. The NCCN Panel endorses the CAP protocol for pathology reporting (www.cap.org) and endorses the ASCO CAP recommendations for quality control performance of HER2 testing and interpretation of IHC and ISH results.[505]

Imaging studies help facilitate image-guided biopsy, delineate locoregional disease, and identify distant metastases. Evaluation of all women suspected with IBC must include diagnostic bilateral mammogram, with the addition of ultrasound as necessary. A breast MRI scan is optional.

Evaluations for the presence of distant metastasis in the asymptomatic patient include liver function testing, bone scan or sodium fluoride PET/CT (category 2B), and diagnostic CT imaging of the chest, abdomen, and pelvis (category 2B; category 2A for diagnostic CT imaging of the chest when pulmonary symptoms are present).

FDG PET/CT may be most helpful in situations where standard imaging results are equivocal or suspicious. However, there is limited evidence suggesting that PET/CT may be a useful adjunct to standard imaging of IBC due to the increased risk of regional lymph node involvement and distant spread of disease in this group of patients.[101,102,604,605] Nevertheless, equivocal or suspicious sites identified by FDG PET/CT scanning or other imaging methods should be biopsied for confirmation of stage IV disease whenever possible. FDG PET/CT is a category 2B recommendation. The consensus of the panel is that FDG PET/CT can be performed at the same time as diagnostic CT. If FDG PET and diagnostic CT are performed and both clearly indicate bone metastases, bone scan or sodium fluoride PET/CT may not be needed.

Genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer as defined by the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.

Treatment

The treatment of patients with IBC should involve a combined modality approach[591] comprising preoperative systemic therapy followed by surgery (mastectomy) and radiotherapy.

Preoperative Chemotherapy

There are no large randomized trials evaluating the optimal systemic treatment of IBC, since it is a rare disease. The systemic therapy recommendations are based on data from retrospective analyses, small prospective studies, and data from non-IBC, locally advanced breast cancer.

The benefit of preoperative systemic therapy followed by mastectomy over preoperative systemic therapy 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.[606] Results from a large retrospective study of patients with IBC performed over a 20-year period at The University of Texas M.D. Anderson Cancer Center 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 DFS rate of 28%.[607]

A retrospective study demonstrated that the addition of a taxane to an anthracycline-based regimen improved PFS and OS in patients with ER-negative IBC.[608] A systematic review found evidence for an association between the intensity of preoperative therapy and the

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likelihood of a pCR.[609] A study of IBC patients, with cytologically confirmed ALN metastases, treated with anthracycline-based chemotherapy with or without a taxane indicated that more patients receiving the anthracycline-taxane combination achieved a pCR compared with those who received only anthracycline-based therapy. In addition, patients who had a pCR in the ALNs had superior OS and DFS compared with those with residual axillary disease.[610]

The NCCN Panel recommends preoperative systemic therapy with an anthracycline-based regimen with or without taxanes for the *initial* treatment of patients with IBC. The panel also recommends completing the planned chemotherapy prior to mastectomy. If the chemotherapy was not completed preoperatively, it should be completed postoperatively.

Targeted Therapy

All women with hormone receptor-positive IBC are recommended to receive endocrine therapy sequentially after completing the planned preoperative systemic therapy.

HER2-positive IBC is associated with a poor prognosis.[595,611] For women with HER2-positive disease, the addition of trastuzumab to primary systemic chemotherapy is associated with better response rates.[612-616] A prospective study that randomized women with locally advanced breast cancers, including those with IBC, to neoadjuvant anthracycline-based chemotherapy with or without trastuzumab for 1 year demonstrated that the addition of trastuzumab significantly improved the response rate and event-free survival.[612] The NCCN Panel recommends inclusion of trastuzumab in the chemotherapy regimen and is recommended for patients with HER2-positive disease. There are no available data to indicate the optimal duration of trastuzumab, specifically among women with IBC. However, based on the available data,[612] the panel recommends continuing trastuzumab therapy for up to 1 year.

Results of small phase II trials indicate that other HER2-targeting agents such as lapatinib and pertuzumab have a clinical benefit in IBC.[367,617] The results of the NEOSPHERE trial that included patients with IBC showed increased pCR with the pertuzumab-containing regimens. Therefore the NCCN Panel has included in a footnote that a pertuzumab-containing regimen may be administered preoperatively in patients with HER2-positive IBC.[367]

Determination of response to neoadjuvant chemotherapy in IBC should include a combination of physical examination and radiologic assessment.

Surgery

Patients with a clinical/pathologic diagnosis of IBC should always be treated with chemotherapy before surgery. It has been known for many years that surgical treatment as *primary* treatment of patients with IBC is associated with poor outcomes.[618] SLN dissection is not a reliable method of assessing ALNs among women with IBC.[619] 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. Breast-conserving therapy is not recommended for patients with IBC.

Mastectomy with level I/II ALN dissection is the recommended surgical procedure recommended by the NCCN Panel for patients who respond to neoadjuvant chemotherapy. The NCCN Panel has listed delayed breast reconstruction as an option that can be recommended to women with IBC who have undergone a modified radical mastectomy.

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Reconstruction of the breasts soon after mastectomy may compromise the post-mastectomy radiation therapy outcomes.[620]

For patients with IBC who *do not* respond to preoperative systemic therapy, mastectomy is not generally recommended. Additional systemic chemotherapy and/or preoperative radiation should be considered for these patients. Patients with tumors responding to this secondary therapy should undergo mastectomy and subsequent treatment as described above.

Radiation

After mastectomy, radiation therapy is recommended after the completion of the planned chemotherapy.

The probability of locoregional lymph node involvement is high for women with IBC. To reduce the risk of local recurrence, the panel recommends radiation therapy to the chest wall and the supraclavicular region. If the internal mammary lymph node(s) is clinically or pathologically involved, radiation therapy should include the internal mammary nodes. If the internal mammary nodes are not clinically or pathologically involved, then including the internal mammary nodes in the radiation therapy field is at the discretion of the treating radiation oncologist (category 3). For HER2-positive disease, trastuzumab may be administered concomitantly with radiation therapy.

Stage IV or Recurrent IBC

Patients with stage IV or recurrent IBC should be treated according to the guidelines for recurrence/stage IV breast cancer (See NCCN Guidelines for Breast Cancer).

Axillary Breast Cancer

Occult breast cancer presenting with axillary metastases is an unusual presentation that can be a diagnostic and therapeutic challenge. Evidence to support recommendations on the management of patients presenting with axillary breast cancer comes from a limited number of retrospective studies involving small numbers of patients[621-623](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.[622,623]

Patients with a suspected occult primary breast cancer will typically present to the oncologist after undergoing an initial biopsy: core needle biopsy (preferred), and/or FNA. Accurate pathologic assessment of the biopsied material is most important. Therefore, the pathologist must be consulted to determine whether the available biopsy material is adequate, or if additional biopsy material is necessary (eg, core needle, incisional, or excisional biopsy) to provide an accurate and complete diagnosis.

Workup for Possible Primary Breast Cancer

MRI of the breast can facilitate the identification of occult breast cancer, and can help select those patients most likely to benefit from mastectomy.[624] 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.[622] In addition, of the 7 patients with a negative MRI who subsequently underwent ALN dissection and radiation therapy to the whole breast, no evidence of local recurrence was evident at a median follow-up of 19 months.

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The NCCN Guidelines for Occult Primary Cancer provide guidance on the diagnosis and initial workup of patients with a suspicious axillary mass without any signs of a primary tumor. A small subset of these patients may have a primary cancer in the axillary tail of the breast. Adenocarcinoma with positive axillary nodes and mediastinal nodes in a woman is highly suggestive of a breast primary. Adenocarcinoma in the supraclavicular nodes, chest, peritoneum, retroperitoneum, liver, bone, or brain could also indicate primary breast cancer in women. The guidelines suggest the use of a mammogram and breast ultrasound for such patients.

Testing for immunohistochemical markers including ER/PR and HER2 is recommended. Elevated ER/PR levels provide strong evidence for a breast cancer diagnosis.[625] MRI of the breast should be considered for a patient with histopathologic evidence of breast cancer when mammography and ultrasound are not adequate to assess the extent of the disease. MRI may be especially helpful in women with dense breast tissue, positive axillary nodes, and suspected occult primary breast tumor or to evaluate the chest wall.[626] Breast MRI has been shown to be useful in identifying the primary site in patients with occult primary breast cancer and may also facilitate breast conservation in selected women by allowing for lumpectomy instead of mastectomy.[622,627] In one report, the primary site was identified using MRI in about half of the women presenting with axillary metastases, irrespective of the breast density.[628]

The NCCN Guidelines for Occult Primary Cancer also provide recommendations for additional workup, 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.

Treatment for Possible Primary Breast Cancer

Patients with MRI-positive breast disease should undergo 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 mastectomy plus axillary nodal dissection or axillary nodal dissection plus whole breast irradiation with or without nodal irradiation. Systemic chemotherapy, endocrine therapy, or trastuzumab is given according to the recommendations for stage II or III disease. 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.

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 outcomes.

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