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Breast Cancer Version 2.2015

Clinical Practice Guidelines in Oncology

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Abstract

Breast cancer is the most common malignancy in women in the United States and is second only to lung cancer as a cause of cancer death. The overall management of breast cancer includes the treatment of local disease with surgery, radiation therapy, or both, and the treatment of systemic disease with cytotoxic chemotherapy, endocrine therapy, biologic therapy, or combinations of these. This portion of the NCCN Guidelines discusses recommendations specific to the locoregional management of clinical stage I, II, and IIIA (T3N1M0) tumors. (J Natl Compr Canc Netw 2015;13:448–475)

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.

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

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 the leading cause of cancer-related death in women.[2]

The lifetime risk of breast cancer for women in the United States has increased from 1 in 11 in the 1970s to 1 in 8 in 2013, a change related to shifting

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Disclosures for the NCCN Breast Cancer Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Breast Cancer Panel members can be found on page 475. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

breast cancer risk factor demographics and the increased use of screening mammography.[3] 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 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 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]

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, axillary lymph node status, tumor hormone receptor (estrogen receptor/progesterone receptor [ER/PR]) content, tumor HER2 status, multigene testing, presence or absence of detectable

Text cont. on page 462.

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CLINICAL STAGE	WORKUP
Stage I T1, N0, M0 or Stage IIA T0, N1, M0 T1, N1, M0 T2, N0, M0 or Stage IIB T2, N1, M0 T3, N0, M0 or Stage IIIA T3, N1, 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 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)

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†Available online, in these guidelines, at NCCN.org.

[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.

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

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[†])

*To view the most recent version of these guidelines, visit NCCN.org.
[†]Available online, in these guidelines, at NCCN.org.

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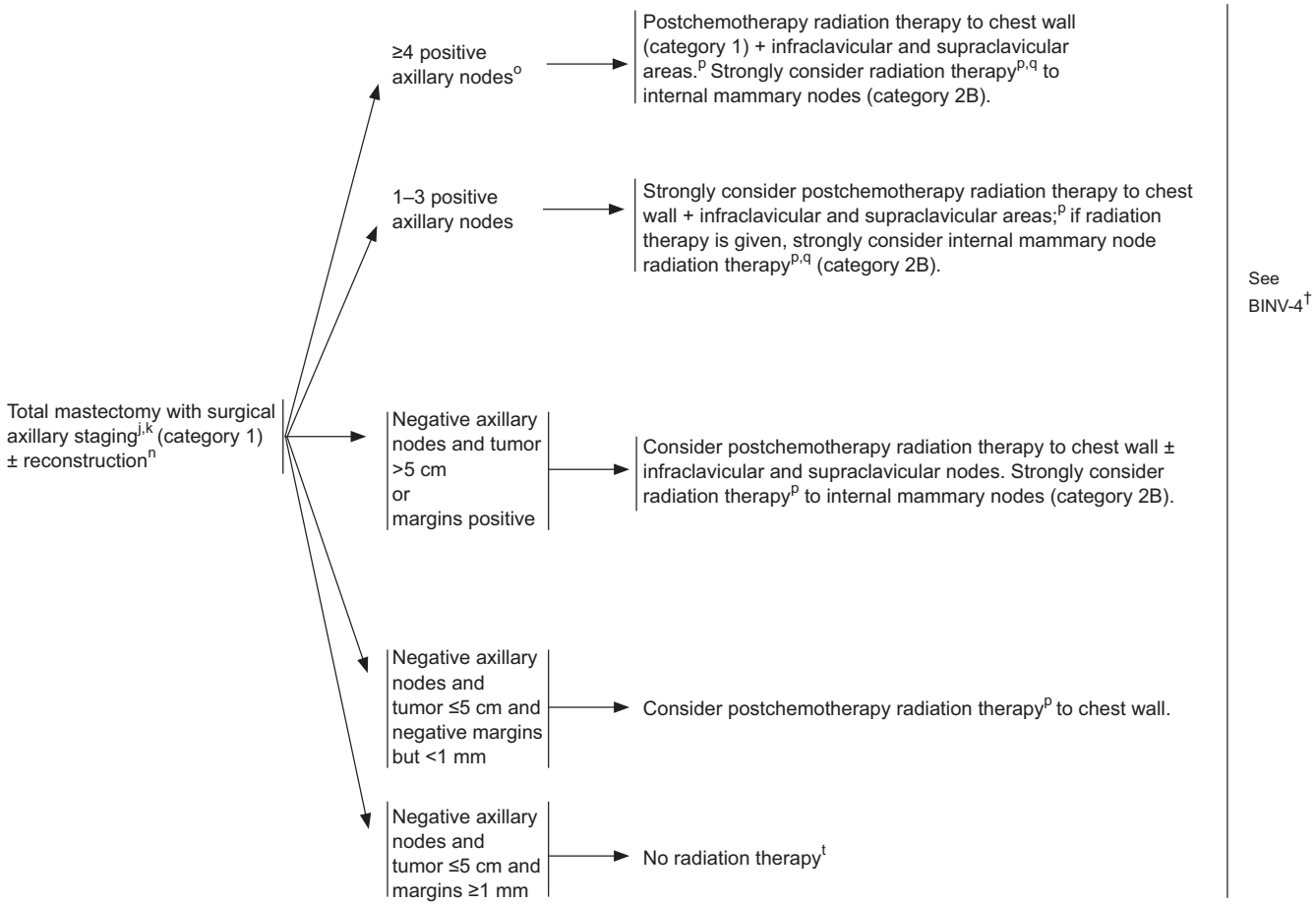
LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3, N1, M0



[†]Available online, in these guidelines, at NCCN.org.

[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.

BINV-3

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.

*To view the most recent version of these guidelines, visit NCCN.org.

[1]Houssami N, Ciatto S, Macaskill P, et al. 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

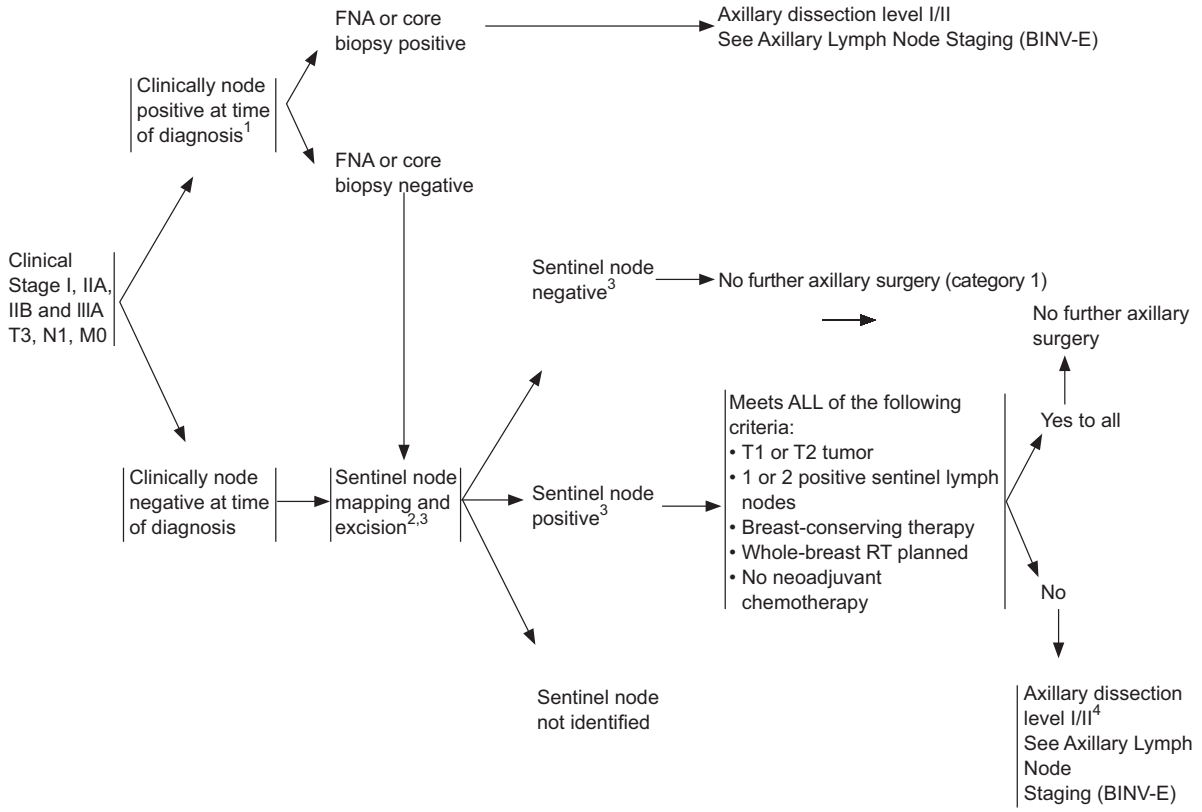
See NCCN Guidelines for Adolescent and Young Adult Oncology*

- 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.

*To view the most recent version of these guidelines, visit NCCN.org.

BINV-C

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



Return to Locoregional Treatment (BINV-2)

[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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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).

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

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, 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;32:1507-1515.
[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*)

*To view the most recent version of these guidelines, visit NCCN.org.

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

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

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.

BINV-H
(2 of 2)

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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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.[6,7] Patient preference is a major component of the decision-making process, especially in situations in which survival rates are equivalent among the available treatment options.

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

Workup

The recommended workup of localized invasive breast cancer includes history and physical examination; a complete blood count, 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 dense breasts in which 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.[8–10] Patients should not be denied the option of breast conservation therapy based on MRI findings alone without additional tissue sampling being performed to verify that these findings represent true malignant disease warranting excision. It also been suggested that MRI use may increase mastectomy rates by identifying mammographically occult disease satellites that would have been adequately treated with postlumpectomy radiation had the disease remain undiscovered without assessing extent of disease using MRI.[11]

Two prospective randomized studies have been performed assessing the utility of MRI for determining extent of disease before surgical resection, and neither showed improvement in postlumpectomy reexcision rates.[12,13] One retrospective study suggested an outcome benefit,[14] whereas another did not.[15] One systematic review[10] documented breast MRI staging to alter surgical treatment in 7.8% to 33.3% of women.[10] However, no differences in outcome, if any, have been demonstrated.

MRI imaging of the breast should be performed 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 status). 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 regarding 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, 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.[16,17] Significant omissions include failure to orient and report surgical margins and failure to report tumor grade consistently. The College of American Pathologists (CAP) 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 Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast and Ovarian, genetic counseling is recommended (to view the most recent version of these guidelines, visit NCCN.org).

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.[18–22] The levels of distress vary from patient to patient and need to be addressed individually. The NCCN Breast Cancer Panel recommends assessing for distress in patients newly diagnosed with breast cancer.

Fertility Counseling

Numerous epidemiologic studies have demonstrated that childbearing after treatment for invasive breast cancer does not increase rates of recurrence or death from breast cancer.[23] 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 after breast cancer therapy.[24–28] No high-level evidence demonstrates that ovarian suppression or other interventions decrease the toxicity of cytotoxic chemotherapy on the premenopausal ovary.[29] However, many women, especially those younger than 35 years, regain menstrual function within 2 years of completing chemotherapy.[30] 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 premenopausal woman with newly diagnosed breast cancer desire to bear children after breast cancer treatment, she should undergo a consultation with a physician with expertise in fertility before the initiation of chemotherapy.[28,31] 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 (to view the most recent version of these guidelines, visit NCCN.org).

Additional Workup Directed by Signs and Symptoms

The panel has reiterated that routine systemic imaging is not indicated for patients with early breast cancer in the absence signs/symptoms of metastatic disease.[32] These recommendations are supported by a study evaluating patients with newly diagnosed breast cancer with bone scan, liver ultrasonography, and chest radiography.[33] 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 on liver ultrasonography or chest radiography in patients with stage I or II disease.[33]

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 Breast Cancer Panel recommends against the use of PET or PET/CT scanning in the staging 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.[34-37]

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 most women with stage I and II breast cancers (category 1).[38–42]

After surgical resection, a careful histological assessment of resection margins is essential. The NCCN Breast Cancer Panel notes that usefulness of lumpectomy is predicated on achieving pathologically negative margins after resection. The 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 ductal carcinoma in situ [DCIS]).[43] For pure DCIS, the definition of negative margins remains a topic of discussion and debate.

If margins remain positive after further surgical reexcisions, then mastectomy may be required for optimal local disease control. In order to adequately assess margins after 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 use of a radiation boost after whole-breast radiation should be considered. Although 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 years, high grade tumor, 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.[44–46] 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.[47] Survival outcomes for young women with breast cancer receiving either lumpectomy or mastectomy are similar.[48]

Only limited data are available on the survival impact of mastectomy contralateral to a unilateral breast cancer.[49] 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 (hazard ratio [HR], 0.68; 95% CI, 0.53–0.88; P=.004).[50] 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%).[50] These differences observed in retrospective analysis could be from selection bias among patients who chose CPM.[51] 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 can-

cer stage groups.[52] Data from a recent meta-analysis found no absolute reduction in risk of distant metastases with contralateral prophylactic mastectomy.[53] 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 contralateral prophylactic mastectomy, no improvement was seen in overall survival of these patients.[53]

The panel recommends that women with breast cancer aged 35 years or younger or who are premenopausal and carriers of a known *BRCA1/2* mutation consider additional risk-reduction strategies after appropriate risk assessment and counseling (see NCCN Guidelines for Breast Cancer Risk Reduction and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian; to view the most recent version of these guidelines, visit NCCN.org). This process should involve multidisciplinary consultations before surgery, and should include a discussion of the risks associated with development of a contralateral breast cancer 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 (T3N1M0) 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 axillary lymph node (ALN) dissection is needed.

The panel recommends sentinel lymph node (SLN) mapping and resection in the surgical staging of the clinically negative axilla to assess the pathologic status of the ALNs in patients with clinical stage I, II, and IIIA (T3N1M0) breast cancer.[54–63] 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 those undergoing standard ALN dissection.[63,64] No significant differences were seen in these studies regarding the effectiveness of the SLN procedure or level I and II dissection for determining the presence or absence of metastases in axillary nodes. However, not all women are candidates for SLN resection. An experienced SLN team is mandatory for the use of SLN mapping and excision.[65,66]

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 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 diagnosis, or a negative core or FNA biopsy of any clinically suspicious ALNs. In many institutions, SLNs are assessed for the presence of metastases by both hematoxylin and eosin (H&E) staining and cytokeratin immunohistochemistry. The clinical significance of a lymph node that is negative on H&E staining but positive on cytokeratin immunohistochemistry is unclear. 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 immunohistochemistry 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 results of a randomized clinical trial (ACOSOG Z0010) of patients with H&E-negative nodes showing that further examination with cytokeratin immunohistochemistry was not associated with improved overall survival over a median of 6.3 years.[67] In the uncommon situation in which H&E staining is equivocal, reliance on the results of cytokeratin immunohistochemistry 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-SLNs.[68–74] Nonetheless, a randomized trial (ACOSOG Z0011) compared SLN resection alone with ALN dissection in women 18 years of age or older with T1/T2 tumors, fewer than 3 positive SLNs, and undergoing breast-

conserving surgery and whole-breast irradiation. In this study, no difference was seen in local recurrence, disease-free survival, or overall survival between the treatment groups. Only ER-negative status, age younger than 50 years, and lack of adjuvant systemic therapy were associated with decreased overall survival.[75] 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 group (n=436; *P*=.11). Median overall survival was approximately 92% in each group.[76] 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 II evaluation of ALN requires that at least 10 lymph nodes should be provided for pathologic evaluation to accurately stage the axilla.[77,78] 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.[79]

Radiation Therapy

Whole-Breast Radiation: Whole-breast radiation reduces the risk of local recurrence and has been shown to have a beneficial effect on survival.[39,42] Randomized trials have demonstrated a decrease in in-breast recurrences with an additional boost dose of radiation (via photons, brachytherapy, or electron beam) to the tumor bed.[80,81] The panel recommends that whole-breast irradiation include most of the breast tissue and that breast irradiation be performed after 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),[82,83] respiratory gating, or prone positioning[84] is recommended.

Dose and Fractionation: Four randomized clinical trials[85–88] have investigated hypofractionated whole-breast radiation schedules (39.0–42.9 Gy in single fractions of 2.6–3.3 Gy) compared with standard 50 Gy in single fractions of 2 Gy. The 10-year follow-up data from the START trials[89] are consistent with the 10-year results of the Canadian trial,[88] which reported that local tumour 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.[88] The START trials reported that radiation-related effects on normal breast tissue, such as breast shrinkage, telangiectasia, and breast edema, were less common with the hypofractionated fraction regimen.[89] The NCCN panel recommends doses of either 45 to 50 Gy in 23 to 25 fractions or 40.0 to 42.5 Gy in 15 to 16 fractions for whole-breast radiation. Based on convenience and the data from the START trials,[89] the short course of radiation therapy (40.0–42.5 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 years, or high-grade disease, or patients with focally positive margins).[90] 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 guideline includes 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," page 461). 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 disease-free survival (HR, 0.68; *P*=.003), and a trend was seen toward improved overall survival (HR, 0.76; *P*=.07).[91]

Accelerated Partial Breast Irradiation: Several studies have been reported using accelerated partial breast irradiation (APBI) rather than whole-breast irradiation after 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.[92] For patients who are not eligible for a clinical trial, 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 radiation therapy.[93] Patients who may be suitable for APBI are women 60 years of age and older who are not carriers of a known *BRCA1/2* mutation and 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. A radiation dose of 34 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 after APBI.[94,95] 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 prechemotherapy tumor characteristics, irrespective of tumor response to preoperative systemic therapy (ie, radiation therapy is recommended in patients with clinical stage III disease and a partial complete response 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 overall survival.[42]

If adjuvant chemotherapy is indicated after lumpectomy, radiation should be given after chemotherapy is completed.[96,97] 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 after radiation therapy or radiation therapy after 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[97]; however, differences in rates of distant or local recurrence were not statistically significant when the 2 arms were compared at 135-month follow-up.[96]

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 disease-free survival.[91] 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 disease-free survival (HR, 0.68; *P*=.003, 5-year risk: 89.7% and 84.0%) and overall survival (HR, 0.76; *P*=.07, 5-year risk: 92.3% and 90.7%).[91] 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 and in those with high-grade invasive ductal carcinoma, the boost dose reduced the local relapse from 19.4% to

11.4% and from 18.9% to 8.6%, respectively.[98] Hence, the panel recommends consideration of a boost to the tumor bed after lumpectomy and whole-breast irradiation. Administration of whole-breast irradiation therapy after 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. One study randomized women with clinical stage I, ER-positive breast cancer who were 70 years of age or older at diagnosis to receive lumpectomy with whole-breast radiation or lumpectomy alone, both with tamoxifen for 5 years. Locoregional recurrence rates were 1% in the lumpectomy, radiation, and tamoxifen arm and 4% in the lumpectomy plus tamoxifen arm. No differences were seen in overall survival, disease-free survival, or need for mastectomy.[99] These results were confirmed in an updated analysis of this study with a median follow-up of 12.6 years.[100] 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.[100] Similar results were obtained in another study of similar design.[101] The NCCN Guidelines allow for the use of lumpectomy (pathologically negative margin required) plus tamoxifen or an aromatase inhibitor without breast irradiation in women 70 years of age or older 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 disease-free and overall survival advantage is conferred by the irradiation of chest wall and regional lymph node in women with positive ALNs after mastectomy and ALN dissection.[102–106] 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 before mastectomy.[107,108]

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.[39] The use of postmastectomy, postchemotherapy 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.[109] 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, because studies do not show an advantage. This is an unusual situation in which high-level evidence exists but is contradictory.[39,104–106,109] Results of an Early Breast Cancer Trialists' Collaborative Group meta-analysis[110] showed 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 therapy was administered. The consensus panel 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.[111] Consideration should be given to radiation to the ipsilateral supraclavicular area and to the ipsilateral internal mammary lymph nodes (category 2B), especially in patients with tumors greater than 5 cm or positive surgical margins.

In patients with node-negative tumors less than 5 cm and clear margins (≥1 mm), postmastectomy radiation therapy is usually not recommended. However, the panel has noted that it may be considered only for patients with a high risk of recurrence. A

retrospective analysis suggests benefit of postmastectomy radiation therapy in reducing risk of recurrence in patients with node-negative disease who have high-risk factors, such as close margins, tumors 2 cm or greater, premenopausal status, and lymphovascular invasion.[112] Another study showed increased risk of locoregional recurrence in women with node-negative triple-negative breast cancer with tumors 5 cm or less.[113]

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 "Principles of Breast Reconstruction Following Surgery," page 460.

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.[114–118] Smoking and obesity are therefore considered relative contraindications 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: Loss of the breast due to mastectomy has implications for breastfeeding, loss of sensation in the skin of the breast and nipple-areolar complex (NAC), and cosmetic, body image, and psychosocial purposes. The cosmetic, body image, and psychosocial issues resulting from loss of the breast may be partially overcome through the performance of breast reconstruction, with or without reconstruction of the NAC.

Many factors must be considered in the decision-making about breast reconstruction. Several different types of breast reconstruction are available that include the use of implants, autogenous tissues, or both.[119–121]

Reconstruction with implants can be performed either through 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.[122] 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 after autogenous tissue breast cancer reconstruction, presumably because of underlying microvascular disease.

Reconstruction can be performed either at the time of the mastectomy and under the same anesthetic, known as *immediate breast reconstruction*, or in a delayed fashion any time after mastectomy, 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 postmastectomy radiation therapy can impact decisions related to breast reconstruction be-

cause there is a significantly increased risk of implant capsular contracture after 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.[123,124] Some studies, however, have not found a significant compromise in reconstruction cosmesis after radiation therapy.[125] The preferred approach to breast reconstruction for these patients was a subject of controversy among the panel. Although some experienced breast cancer teams have used 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 implants can be performed before radiation or after completion of radiation therapy.

In a previously radiated patient, the use of tissue expanders/implants is relatively contraindicated.[126] Tissue expansion of irradiated skin can result in a significantly increased risk of capsular contracture, malposition, poor cosmesis, implant exposure, and failed reconstruction.[127,128] 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 most of the original skin envelope. These 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 after mastectomy, although the impact of this procedure on these quality-of-life issues has not been well studied.[129–131] 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.[130,132,133] 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 is peripherally located in the breast (>2 cm from nipple).[134,135] Contraindications for nipple preservation include evidence of nipple involvement, such as Paget 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,[136] 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.[137–141] 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 procedures in relation to adjuvant therapies, and perform a resection that achieves appropriate surgical margins. Postmastectomy radiation should still be applied for patients treated by skin-sparing mastectomy following the same selection criteria as for standard mastectomy.

Breast Reconstruction After Lumpectomy: Issues related to breast reconstruction also pertain to women who undergo or have undergone a lumpectomy, particularly in situations in which the surgical defect is large and/or expected to be cosmetically unsatisfactory. The likely cosmetic outcome of lumpectomy should be evaluated before surgery. Oncoplastic techniques for breast conservation can extend breast-conserving surgical options in situation in which the resection itself would likely yield an unacceptable cosmetic outcome.[142] The evolving field of oncoplastic surgery includes the use of "volume displacement" techniques performed in conjunction with a large partial mastectomy.[143] 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.[143,144]

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.[145]

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 before 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.

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Benjamin O. Anderson, MD	None	Merz, Inc.	None	2/24/15
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Sarah L. Blair, MD	None	None	None	1/21/15
Harold J. Burstein, MD, PhD	None	None	None	9/16/14
Amy Cyr, MD	None	None	None	2/24/15
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Matthew Goetz, MD	Eli Lilly and Company	Eli Lilly and Company	None	11/12/14
Lori J. Goldstein, MD	Novartis Pharmaceuticals Corporation; Dompé Pharmaceuticals; and Roche Laboratories, Inc.	None	Novartis Pharmaceuticals Corporation; and Synta Pharmaceuticals Corp.	2/12/15
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[a]The following have disclosed an Employment/Governing Board, Patent, Equity, or Royalty conflict:
Clifford A. Hudis, MD: ASCO and Breast Cancer Research Foundation
Lori J. Pierce, MD: PFS Genomics and UpToDate
Lee S. Schwartzberg, MD: Caris Life Sciences, Ltd.
Mary Lou Smith, JD, MBA: Gateway for Cancer Research Foundation and National Accreditation Program for Breast Centers

[b]The following have disclosed a Spouse/Domestic Partner/Dependent Potential conflict:
Karen Lisa Smith, MD, MPH: Abbott Laboratories; Merck & Co., Inc.; AbbVie Inc.; Express Scripts; and Hospira, Inc.

The NCCN Guidelines staff have disclosed that they have no conflicts of interest.