

## NCCN

# Invasive Breast Cancer Version 1.2016

## Clinical Practice Guidelines in Oncology

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## Overview

The American Cancer Society estimates that 249,260 Americans will be diagnosed with invasive breast cancer and 40,890 will die of the disease in the United States in 2016.<sup>1</sup> Breast cancer is the most frequently diagnosed cancer globally and the leading cause of cancer-related death in women.<sup>2</sup>

The cause of most breast cancer cases is unknown. However, numerous risk factors for the

### 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 article outlines the NCCN Guidelines specific to breast cancer that is locoregional (restricted to one region of the body), and discusses the management of clinical stage I, II, and IIIA (T3N1M0) tumors. For NCCN Guidelines on systemic adjuvant therapy after locoregional management of clinical stage I, II and IIIA (T3N1M0) and for management for other clinical stages of breast cancer, see the complete version of these guidelines at NCCN.org.

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### 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.

### Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Breast Cancer are not printed in this issue of JNCCN but can be accessed online at NCCN.org.**

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### Disclosures for the 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 354. (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.

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disease have been established. These risk factors include female sex; increasing patient age, family history of breast cancer at a young age, early menarche, late menopause, nulliparity, older age at first live child-birth, prolonged combined hormone replacement therapy, previous exposure to therapeutic chest wall irradiation, benign proliferative breast disease, increased mammographic breast density, and genetic mutations, including the *BRCA1/2* genes (see the NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Breast Cancer Risk Reduction, available at NCCN.org). However, except for female sex 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  $\geq 1.7\%$  5-year risk for breast cancer using the Gail model of risk assessment<sup>3</sup>) may consider risk reduction strategies (see the NCCN Guidelines for Breast Cancer Risk Reduction at NCCN.org).

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.<sup>4</sup> The invasive ductal carcinomas include unusual variants of breast cancer, such as mucinous, adenoid cystic, and tubular carcinomas, which have especially favorable natural histories.

Text cont. on page 339.

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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
  - Diagnostic bilateral mammogram; ultrasound as necessary
  - Pathology review<sup>a</sup>
  - Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER2 status<sup>b</sup>
  - Genetic counseling if patient is high risk for hereditary breast cancer<sup>c</sup>
  - Breast MRI<sup>d</sup> (optional), with special consideration for mammographically occult tumors
  - Fertility counseling if premenopausal<sup>e</sup>
  - Assess for distress<sup>f</sup>
- For clinical stage I-IIB, consider additional studies only if directed by signs or symptoms:<sup>g</sup>
- CBC
  - Liver function tests and alkaline phosphatase
  - 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:
- CBC
  - Liver function tests and alkaline phosphatase
  - Chest diagnostic CT
  - Abdominal ± pelvic diagnostic CT or MRI
  - Bone scan or sodium fluoride PET/CT<sup>h</sup> (category 2B)
  - FDG PET/CT<sup>i,j</sup> (optional, category 2B)

<sup>a</sup>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>.

<sup>b</sup>See Principles of HER2 Testing (BINV-A; available online, in these guidelines, at NCCN.org).

<sup>c</sup>See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian (available at NCCN.org).

<sup>d</sup>See Principles of Dedicated Breast MRI Testing (BINV-B).

<sup>e</sup>See Fertility and Birth Control (BINV-C).

<sup>f</sup>See NCCN Guidelines for Distress Management.

<sup>g</sup>Routine systemic staging is not indicated for early breast cancer in the absence of symptoms.

<sup>h</sup>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.

<sup>i</sup>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 stage 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.

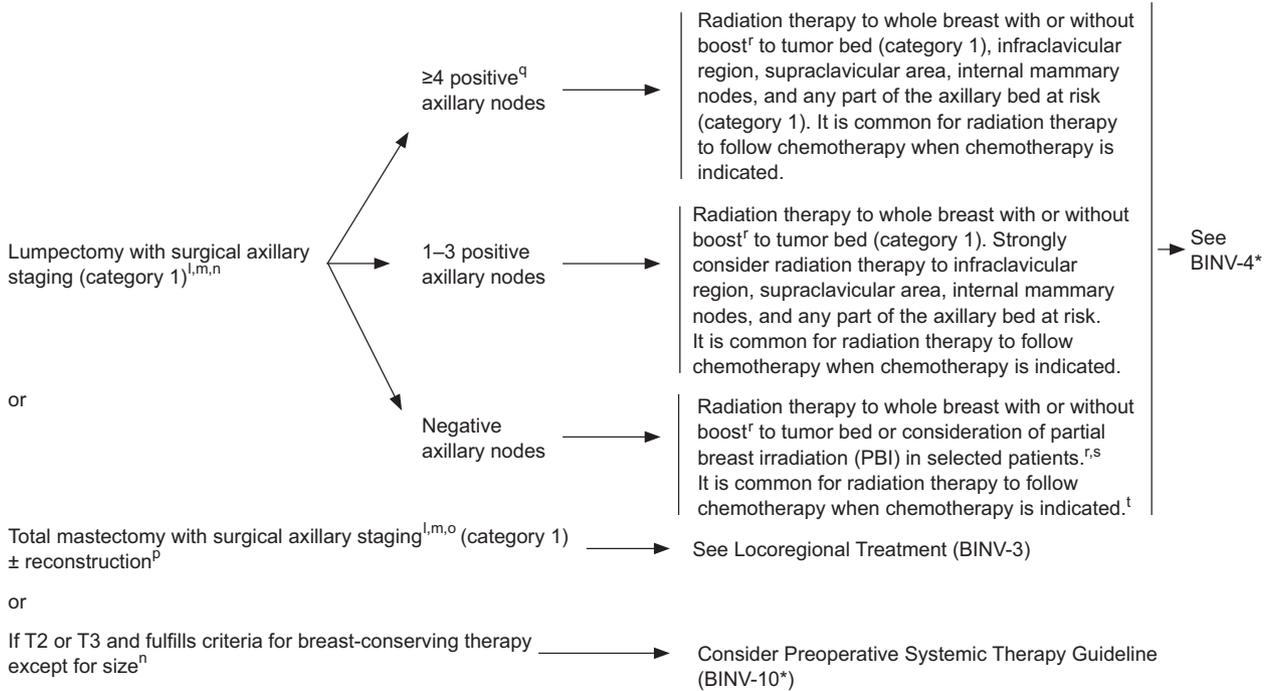
<sup>j</sup>FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.

<sup>k</sup>See NCCN Guidelines for Older Adult Oncology for special treatment considerations (available at NCCN.org).

BINV-1

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LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3, N1, M0<sup>k</sup>

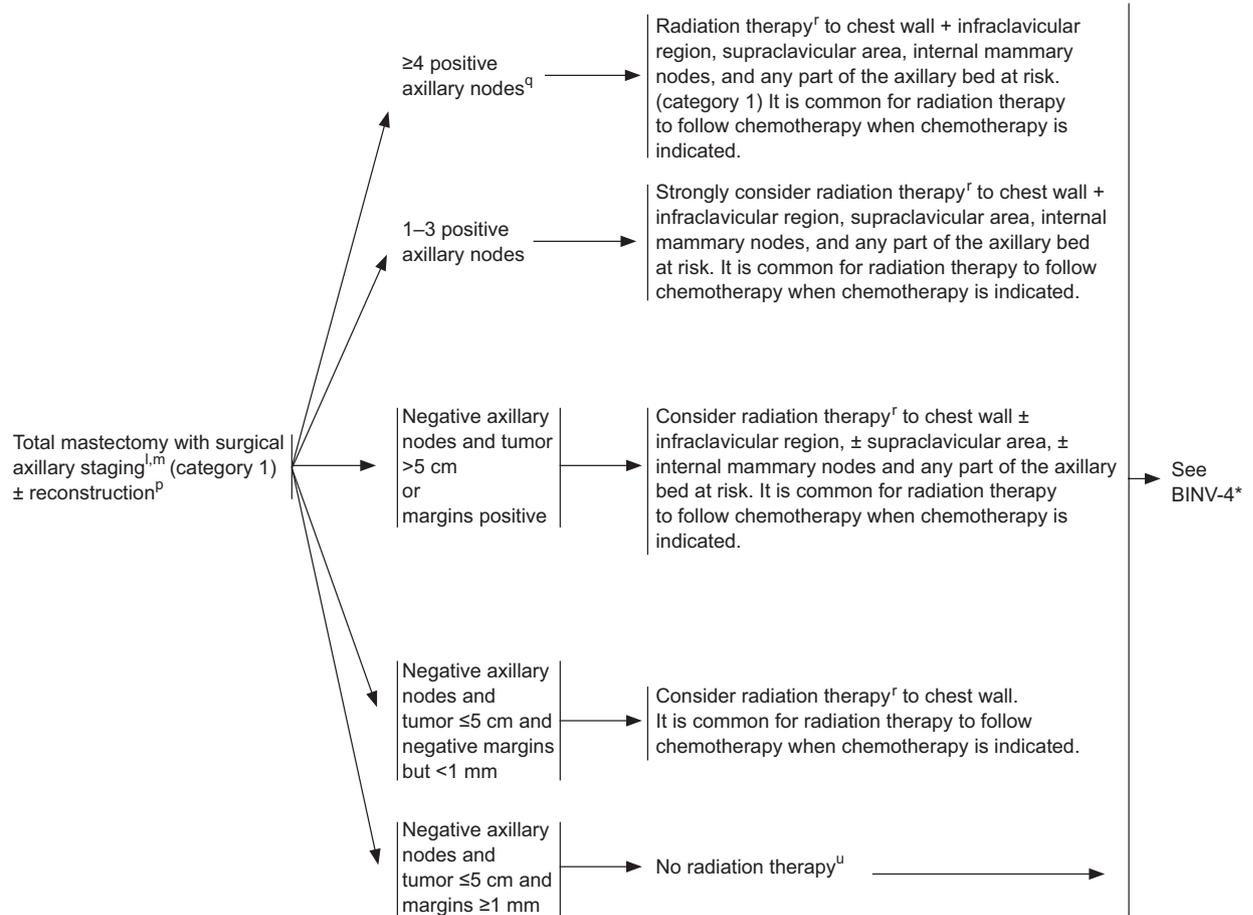


\*Available online, in these guidelines, at NCCN.org

<sup>k</sup>See NCCN Guidelines for Older Adult Oncology for special treatment considerations.  
<sup>l</sup>See Surgical Axillary Staging (BINV-D).  
<sup>m</sup>See Axillary Lymph Node Staging (BINV-E) and Margin Status in Infiltrating Carcinoma (BINV-F).  
<sup>n</sup>See Special Considerations to Breast-Conserving Therapy Requiring Radiation Therapy (BINV-G).  
<sup>o</sup>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 (available at NCCN.org), 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.  
<sup>p</sup>See Principles of Breast Reconstruction Following Surgery (BINV-H).  
<sup>q</sup>Consider imaging for systemic staging, including diagnostic CT or MRI, bone scan, and optional FDG PET/CT (category 2B) (See BINV-1).  
<sup>r</sup>See Principles of Radiation Therapy (BINV-I).  
<sup>s</sup>PBI may be administered prior to chemotherapy.  
<sup>t</sup>Breast irradiation may be omitted in patients ≥70 y of age with estrogen-receptor positive, clinically node-negative, T1 tumors who receive adjuvant endocrine therapy (category 1).

BINV-2

LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3, N1, M0<sup>k</sup>



\*Available online, in these guidelines, at NCCN.org

<sup>k</sup>See NCCN Guidelines for Older Adult Oncology for special treatment considerations (available at NCCN.org).

<sup>l</sup>See Surgical Axillary Staging (BINV-D).

<sup>m</sup>See Axillary Lymph Node Staging (BINV-E) and Margin Status in Infiltrating Carcinoma (BINV-F).

<sup>p</sup>See Principles of Breast Reconstruction Following Surgery (BINV-H).

<sup>q</sup>Consider imaging for systemic staging, including diagnostic CT or MRI, bone scan, and optional FDG PET/CT (category 2B) (See BINV-1).

<sup>r</sup>See Principles of Radiation Therapy (BINV-I).

<sup>u</sup>Postmastectomy radiation therapy may be considered for patients with multiple high-risk recurrence factors.

BINV-3

## Invasive Breast Cancer, Version 1.2016

### 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 (available at NCCN.org).

#### Personnel, Facility, and Equipment

- Breast MRI examinations are performed with IV contrast and 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 image-guided 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.<sup>1</sup>
- May be helpful for breast cancer evaluation before and after preoperative systemic 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.

<sup>1</sup>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.

BINV-B

## FERTILITY AND BIRTH CONTROL

See NCCN Guidelines for Adolescent and Young Adult Oncology (available at [NCCN.org](http://NCCN.org))

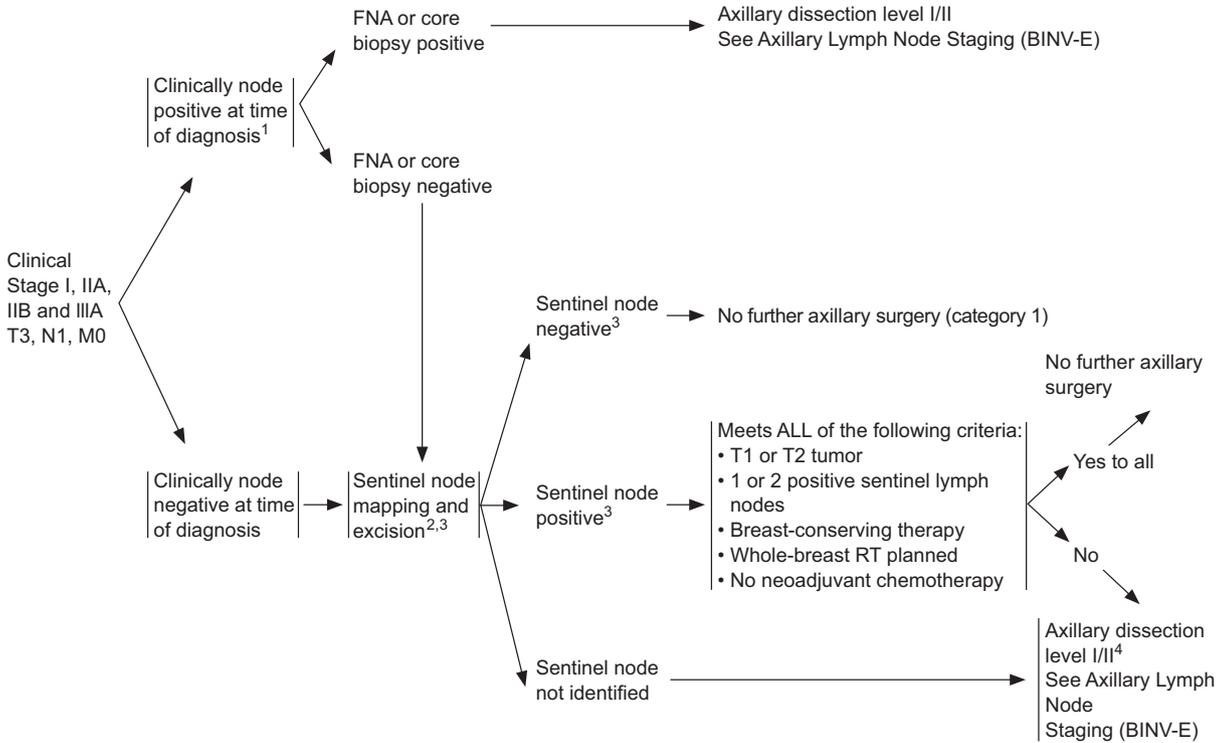
- All premenopausal patients should be informed about the potential impact of chemotherapy on fertility and asked about their desire for potential future pregnancies. Patients who may desire future pregnancies should be referred to fertility specialists before chemotherapy and/or endocrine therapy to discuss the options based on patient specifics, disease stage, and biology (which determine the urgency and type and sequence of treatment). Timing and duration allowed for fertility preservation, options inclusive of oocyte and embryo cryopreservation as well as evolving technologies, and the probability of successful pregnancies subsequent to completion of breast cancer therapy are also to be discussed.
- 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.

BINV-C

**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.

Invasive Breast Cancer, Version 1.2016

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



<sup>1</sup>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.  
<sup>2</sup>Sentinel lymph node mapping injections may be peritumoral, subareolar, or subdermal.  
<sup>3</sup>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.  
<sup>4</sup>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-D

**AXILLARY LYMPH NODE STAGING**

SLNB should be performed and is the preferred method of axillary lymph node staging if the patient is an appropriate SLNB candidate (See BINV-D).

In the absence of definitive data demonstrating superior survival, the performance of axillary staging may be considered optional in patients who have particularly favorable tumors, patients for whom the selection of adjuvant systemic and/or radiation therapy is unlikely to be affected, 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 and/or III. 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).

BINV-E

## Invasive Breast Cancer, Version 1.2016

### 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.<sup>1</sup> 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).<sup>2</sup> 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 for recurrence. 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

<sup>1</sup>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.

<sup>2</sup>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.

BINV-F

## 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
- Diffusely positive pathologic margins<sup>1</sup>

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)
- Positive pathologic margin<sup>1</sup>
- 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 Genetic/Familial High-Risk Assessment Breast and Ovarian; available at [NCCN.org](http://NCCN.org)).

<sup>1</sup>See Margin Status in Infiltrating Carcinoma (BINV-F).

BINV-G

## Invasive Breast Cancer, Version 1.2016

### 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 or the scope of appropriate surgical treatment for this disease. Coordinating consultation and surgical treatment with a reconstructive surgeon should be executed within a reasonable time frame. 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 by 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.

BINV-H  
(1 OF 2)

## PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY (cont.)

- 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.
- 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 other nipple discharge associated with malignancy, and/or imaging findings suggesting malignant involvement of the nipple or subareolar tissues 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)

## Invasive Breast Cancer, Version 1.2016

### PRINCIPLES OF RADIATION THERAPY

#### Optimizing Delivery of Individual Therapy:

It is important to individualize radiation therapy planning and delivery. CT-based treatment planning is encouraged to delineate target volumes and adjacent organs at risk. Greater target dose homogeneity and sparing of normal tissues can be accomplished using compensators such as wedges, forward planning using segments, and intensity-modulated radiation therapy (IMRT). Respiratory control techniques including deep inspiration breath-hold and prone positioning may be used to try to further reduce dose to adjacent normal tissues, in particular heart and lung. Boost treatment in the setting of breast conservation can be delivered using enface electrons, photons, or brachytherapy. Chest wall scar boost when indicated is typically treated with electrons or photons. Verification of daily setup consistency is done with weekly imaging. In certain circumstances, more frequent imaging may be appropriate. Routine use of daily imaging is not recommended.

#### Whole Breast Radiation:

Target definition is the breast tissue in entirety. The whole breast should receive a dose of 46–50 Gy in 23–25 fractions or 40–42.5 Gy in 15–16 fractions (hypofractionation is preferred). All dose schedules are given 5 days per week. A boost to the tumor bed is recommended in patients at higher risk for recurrence. Typical boost doses are 10–16 Gy in 4–8 fractions.

#### Chest Wall Radiation (including breast reconstruction):

The target includes the ipsilateral chest wall, mastectomy scar, and drain sites when indicated. Depending on whether the patient has had breast reconstruction 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. Dose is 46–50 Gy in 23–25 fractions to the chest wall +/- scar boost at 2 Gy per fraction to a total dose of approximately 60 Gy. All dose schedules are given 5 days per week. Special consideration should be given to the use of bolus material 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 patient anatomy. For internal mammary node identification, the internal mammary artery and vein can be used as a surrogate for the nodal location (as the nodes themselves are not usually visible on planning imaging). Based on the post-mastectomy radiation randomized studies and recent trials, radiation therapy of the internal mammary lymph nodes should be strongly considered when delivering regional nodal irradiation. CT treatment planning should be utilized when treating the internal mammary lymph nodal volume to evaluate dose to normal tissues, especially the heart and lung, and dose constraints respected. Dose is 46–50 Gy in 23–25 fractions to the regional nodal fields. All dose schedules are given 5 days per week.

#### 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. 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 is prescribed to the tumor bed. Other fractionation schemes are currently under investigation.

#### Preoperative Systemic Therapy:

In patients treated with preoperative systemic therapy, indications for radiation therapy and treatment fields should be based on the maximum stage from the pre-therapy clinical stage, pathologic stage, and tumor characteristics.

BINV-I

#### DEFINITION OF MENOPAUSE

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

- Prior bilateral oophorectomy
- Age  $\geq 60$  y
- Age  $< 60$  y and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and 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.

BINV-M

**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.

Cont. from page 325.

## 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 (ALN) status, tumor hormone receptor (estrogen receptor [ER]/progesterone receptor [PR]) content, tumor HER2 status, multigene testing, presence or absence of detectable metastatic disease, patient comorbid conditions, patient age, and menopausal status. One percent of breast cancers occur in men, and men with breast cancer should be treated similarly to postmenopausal women, except that tamoxifen is the preferred adjuvant treatment.<sup>5-9</sup> There are limited clinical data on the efficacy of single-agent aromatase inhibitors in men, and aromatase inhibitors may be combined with gonadotropin-releasing hormone analogues for more complete estradiol suppression. Patient preference is a major component of the decision-making process, especially when 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 and ductal carcinoma in situ (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.

## Stage I, IIA, IIB, or IIIA (T3N1M0)

### Workup

The recommended workup of localized invasive breast cancer includes a history and physical examination; bilateral diagnostic mammography; breast ultrasonography, if necessary; determination of tumor hormone receptor status (ER and PR determinations); determination of HER2 receptor status; and pathology review. A CBC and liver function

tests (LFTs) have no added benefit in the detection of underlying metastatic disease in patients with asymptomatic early-stage breast cancer.<sup>10</sup> In addition, monitoring of disease relapse with any tumor markers is not recommended.

Use of MRI is optional and 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 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, resulting in further diagnostic workup in many circumstances, including MRI-guided biopsy.<sup>11-13</sup> MRI findings tend to overestimate extent of disease,<sup>14</sup> resulting in an increased frequency of mastectomies.<sup>15-18</sup>

MRI findings alone are insufficient to determine whether breast conservation therapy is optimal, because additional tissue sampling is needed to verify true malignant disease warranting excision. MRI use may increase mastectomy rates by identifying mammographically occult disease satellites that would have been adequately treated with postlumpectomy radiation had the disease remained undiscovered without MRI.<sup>18</sup>

Two prospective randomized studies examined the utility of preoperative MRI in determining disease extent, and neither demonstrated improvement in rates of postlumpectomy re-excision.<sup>19,20</sup> A retrospective review of MRIs showed conflicting outcome results, one with benefit<sup>21</sup> and one without.<sup>22</sup> Although one systematic review<sup>13</sup> documented that breast MRI staging altered surgical treatment in 7.8% to 33.3% of women,<sup>13</sup> no differences in local recurrence or survival have yet been shown. In addition, no evidence shows that use of breast MRI increases rates of margin-negative resection.<sup>23,24</sup>

If breast MRI is performed, a dedicated breast coil, an imaging team experienced with MRI-guided breast biopsy, and a multidisciplinary treatment team are the standard of care. Clinically positive axillary nodes and occult primary breast cancer or Paget's disease of the nipple with breast primary not identified on mammography, ultrasound, or physical examination are specific indications for breast MRI. MRI may also be useful for evaluating breast cancer response to preoperative systemic therapy and assessing the potential for breast-conserving therapy.

**Pathology Assessment:** Full knowledge of extent of disease and biologic features is central to the treatment of breast cancer. Several factors contribute to the determination of the disease staging, recurrence risk assessment, and predictive response (eg, ER, PR, HER2). The excised tissue detailing the written pathology report details these key factors. The accuracy of pathology reporting requires communication between the clinician and the pathologist relating pertinent patient history, prior breast biopsies, prior chest irradiation, pregnancy status, biopsy characteristics (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.<sup>25,26</sup> 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 ([www.cap.org](http://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:** Genetic counselling is recommended 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 (to view the most recent version of these guidelines, visit [NCCN.org](http://NCCN.org)).

**Distress Assessment:** Levels of distress may vary in patients and should be addressed individually. Psychological distress can be impacted by body image and other factors. Younger women have higher rates of psychosocial distress than those diagnosed at older ages.<sup>27-31</sup> The NCCN panel recommends accessing 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.<sup>32</sup> 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.

Many women, especially those younger than age 35 years, regain menstrual function within 2 years of completing chemotherapy.<sup>33</sup> 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.

A decision for fertility preservation should include multiple factors, such as patient preference, tumor stage and biology, age of the patient, risk of premature ovarian failure based on anticipated type and duration of chemotherapy and/or endocrine therapy, and the timing and duration allowed for fertility preservation. Several studies report lower rates of fertility discussion among female patients with cancer,<sup>34-36</sup> despite the updated ASCO guidelines stating that patients should be not excluded from consideration of discussion about fertility preservation for any reason, including parity, prognosis, age, and socioeconomic status.<sup>37</sup> The NCCN panel recommends that all women of childbearing potential should have a discussion with their treating physicians. Patients who desire to bear children after systemic therapy should be referred to a fertility specialist before starting systemic (chemotherapy or endocrine) therapy.<sup>37-43</sup>

Randomized trials have shown that gonadotropin-releasing hormone (GnRH) agonists (such as goserelin) administered before initiation of chemotherapy and then concurrently with adjuvant chemotherapy protect against ovarian failure and reduce the risk of early menopause.<sup>44-47</sup> In one trial, goserelin improved the probability of pregnancy from 11% to 21% in patients with hormone receptor–negative early-stage breast cancer.<sup>47</sup> Smaller historical experiences in patients with hormone receptor–positive disease have conflicting results with respect to the protective effects of GnRH agonists in fertility preservation.

Patients should be informed of all the various modalities available to minimize gonadal damage and preserve ovarian function and future fertility. The fertility specialist should discuss the specifics of

fertility preservation options, including the types of hormonal interventions and the risks involved with ovarian stimulation, embryo or oocyte cryopreservation, and other investigational options, and the probability of successful gestation and childbirth.<sup>48,49</sup>

Combining the various modalities for a specific patient may increase the odds of preservation of future fertility. It is important for fetal safety that women actively avoid becoming pregnant during breast cancer treatment. Also see the NCCN Guidelines for Adolescent and Young Adult Oncology at NCCN.org.

### Additional Workup

The panel has reiterated that routine systemic imaging is *not* indicated for patients with early-stage breast cancer in the absence of signs/symptoms of metastatic disease.<sup>50</sup> These recommendations are based on studies showing no additional value of these tests in patients with early-stage disease.<sup>51-53</sup> In one study, 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.<sup>51</sup> For patients with stage III breast cancer, the prevalence of positive results on liver ultrasound and chest radiography was 6% and 7%, respectively.<sup>51</sup>

For patients presenting with disease confined to the breast (stage I–II) the NCCN panel does not recommend routine systemic imaging in the absence of signs or symptoms suspicious for metastatic disease. According to the panel, additional tests may be considered in patients who present with locally advanced disease (T3N1–3M0) and in those with signs or symptoms suspicious for metastatic disease.

A CBC and LFTs may be considered if the patient is a candidate for preoperative systemic therapy, or if these tests are otherwise clinically indicated. Additional tests may be considered only based on the signs and symptoms.

A chest diagnostic CT is indicated only if pulmonary symptoms (eg, cough or hemoptysis), are present. Likewise, abdominal imaging using diagnostic CT or MRI is indicated if the patient has an elevated alkaline phosphatase level, abnormal results on LFTs, abdominal symptoms, or an abnormal physical examination of the abdomen or pelvis.

A bone scan is indicated in patients presenting with localized bone pain or an elevated alkaline

phosphatase level. The use of PET or PET/CT scanning is not indicated in the routine staging of clinical stage I, II, or operable III (T3N1) breast cancer. 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 detecting axillary nodal metastases, the low prior probability of these patients having detectable metastatic disease, and the high rate of false-positive scans.<sup>54-57</sup> PET/CT is a category 2B recommendation for patients with stage IIIA disease. FDG PET/CT is most helpful when standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.

### Locoregional Treatment Surgery

In general, patients with early-stage breast cancer undergo primary surgery (lumpectomy or mastectomy) with or without radiation therapy. Following local treatment, adjuvant systemic therapy may be offered based on primary tumor characteristics, such as tumor size, grade, lymph node involvement, ER/PR status, and expression of HER2 receptor.

Several randomized trials document that mastectomy is equivalent to breast-conserving therapy (lumpectomy with whole breast irradiation) with respect to survival as primary breast local treatment for most women with stage I and II breast cancers (category 1).<sup>58-62</sup>

After surgical resection, a careful histologic assessment of resection margins is essential. The NCCN panel notes that benefit 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/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).<sup>63</sup>

If margins remain positive after further surgical re-excisions, then mastectomy may be required for optimal local disease control.

To adequately assess margins after surgery, the panel recommends that the surgical specimens be directionally oriented and that the pathologist provide descriptions of the gross and microscopic mar-

gin 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.

### Breast-Conserving Therapy (Lumpectomy)

Lumpectomy allows patients to preserve the breast without sacrificing oncologic outcome. 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 diffusely 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 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.<sup>64–66</sup> Risk factors, such as a family history of breast cancer or a genetic predisposition for breast cancer (ie, *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.<sup>67</sup> Studies have shown that survival outcomes are similar for young women with breast cancer receiving either lumpectomy or mastectomy.<sup>60,61,68–70</sup> Some recent studies show improved survival<sup>71–73</sup> and fewer post-surgical complications<sup>74</sup> with lumpectomy.

### Mastectomy

Mastectomy is indicated for patients who are not candidates for lumpectomy and those who choose this procedure over lumpectomy.

Only limited data are available on the survival impact of risk-reducing contralateral mastectomy in women with a unilateral breast cancer.<sup>75</sup> Analysis of women included in the SEER database treated

with mastectomy for a unilateral breast cancer from 1998 to 2003 showed that contralateral mastectomy 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, 0.68; 95% CI, 0.53–0.88;  $P=.004$ ).<sup>76</sup> 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%).<sup>76</sup> These differences observed in retrospective analysis could be due to selection bias among patients who chose risk-reducing contralateral mastectomy.<sup>77</sup> A statistical simulation of survival outcomes after risk-reducing contralateral mastectomy among women with stage I or II breast cancer with no *BRCA* mutation found that the absolute 20-year survival benefit from risk-reducing contralateral mastectomy was less than 1% among all age, ER status, and cancer stage groups.<sup>78</sup> Data from a recent meta-analysis found no absolute reduction in risk of distant metastases with risk-reducing mastectomy.<sup>79</sup> 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 risk-reducing contralateral mastectomy, no improvement was seen in overall survival (OS) of these patients.<sup>79</sup>

The NCCN panel recommends that women with breast cancer who are aged 35 years or younger, 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, available at NCCN). 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, risk-reduction 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.

The NCCN panel recommends referring to the NCCN Guidelines for Older Adult Oncology for special considerations regarding this population (to view the most recent version of these guidelines, visit [NCCN.org](http://NCCN.org)).

### 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)<sup>80</sup> or core biopsy must be considered in patients with clinically positive nodes to determine whether ALN dissection is needed.

Performance of sentinel lymph node (SLN) mapping and resection in the surgical staging of the clinically negative axilla is recommended and preferred by the panel for assessment of the pathologic status of the ALNs in patients with clinical stage I, II, and IIIA (T3N1M0) breast cancer.<sup>81–90</sup> 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.<sup>90,91</sup> 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.<sup>92,93</sup> 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 ALNs. SLNs can be assessed for the presence of metastases by both hematoxylin and eosin (H&E) staining and cytokeratin immunohistochemistry (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 treat-

ment decisions should be made based solely on H&E staining. This recommendation is further supported by results of a randomized clinical trial (ACOSOG Z0010) in patients with H&E-negative nodes which showed that further examination by cytokeratin IHC was not associated with improved OS over a median of 6.3 years.<sup>94</sup> 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 nonsentinel nodes.<sup>95–101</sup>

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 (DFS), or OS between the treatment groups. Only ER-negative status, age younger than 50 years, and lack of adjuvant systemic therapy were associated with decreased OS.<sup>102</sup> 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 OS was approximately 92% in each group.<sup>103</sup> Therefore, based on these results after SLN mapping and excision, if a patient has T1 or T2 tumor with 1 to 2 positive SLNs, did not undergo preoperative systemic therapy, was treated with lumpectomy, and will receive whole breast radiation, the panel recommends no further axillary surgery.

The panel recommends level I or II axillary dissection when (1) patients have clinically positive nodes at the time of diagnosis that is confirmed by FNA or core biopsy; or (2) 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 be provided for pathologic evaluation to accurately stage the axilla.<sup>104,105</sup> ALN should be extended to include level III

nodes only if gross disease is apparent in the level II or III 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 showing 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.<sup>106</sup>

## Radiation Therapy

### Planning Techniques, Targets, and Doses

It is important to individualize radiation therapy planning and delivery. CT-based treatment planning is encouraged to delineate target volumes and adjacent organs at risk. Greater target dose homogeneity and sparing of normal tissues can be accomplished using compensators such as wedges, forward planning using segments, and intensity-modulated radiation therapy (IMRT). Respiratory control techniques, including deep inspiration breath-hold and prone positioning, may be used to try to further reduce dose to adjacent normal tissues, in particular heart and lung. Boost treatment in the setting of breast conservation can be delivered using enface electrons, photons, or brachytherapy. Chest wall scar boost when indicated is typically treated with electrons or photons. Verification of daily setup consistency is done with weekly imaging. In certain circumstances, more frequent imaging may be appropriate. Routine use of daily imaging is not recommended.

### Whole Breast Radiation

Whole breast radiation reduces the risk of local recurrence and has been shown to have a beneficial effect on survival.<sup>59,62</sup> Randomized trials have shown decreased in-breast recurrences with an additional boost dose of radiation (by photons, brachytherapy, or electron beam) to the tumor bed.<sup>107,108</sup> The panel recommends whole breast irradiation to include breast tissue in entirety. CT-based treatment plan-

ning is recommended to limit irradiation exposure of the heart and lungs and to assure adequate coverage of the breast and lumpectomy site.

For greater homogeneity of target dose and to spare normal tissues, compensators such as tissue wedges, forward planning using segments, and IMRT may be used.<sup>109,110</sup> Respiratory control techniques, including deep inspiration breath-hold and prone positioning, may be used to try to further reduce dose to adjacent normal tissues, in particular heart and lung.<sup>111</sup> Radiation boost treatment in the setting of breast conservation can be delivered using enface electrons, photons, or brachytherapy.

### Dose and Fractionation

Four randomized clinical trials have investigated hypofractionated whole breast radiation schedules (39–42.9 Gy in single fractions of 2.6–3.3 Gy) compared with standard 50 Gy in single fractions of 2 Gy.<sup>112–115</sup> The 10-year follow-up data from the START trials<sup>116</sup> are consistent with the 10-year results of the Canadian trial,<sup>115</sup> 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.<sup>115</sup> 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.<sup>116</sup> The NCCN panel recommends a dose of 46 to 50 Gy in 23 to 25 fractions or 40 to 42.5 Gy in 15 to 16 fractions for whole breast irradiation. Based on convenience and the data from the START trials,<sup>116</sup> the short course of radiation therapy (40–42.5 Gy in 15–16 fractions) is the NCCN-preferred option for treatment of the breast in patients being irradiated to the breast only. A boost to the tumor bed is recommended in patients with higher-risk characteristics (such as age <50 years, high-grade disease, or focally positive margins) to reduce local relapse.<sup>108,116–120</sup> Typical boost doses are 10 to 16 Gy in 4 to 8 fractions.

**Chest Wall Radiation (Including Breast Reconstruction):** The target includes the ipsilateral chest wall, mastectomy scar, and drain sites when indicated. Depending on whether the patient has had breast reconstruction, several techniques using photons and/or electrons are appropriate. The NCCN panel recommends a dose of 46 to 50 Gy in 23 to 25 fractions to the chest wall. A boost to the scar at the dose of 2 Gy per fraction to a total dose of ap-

proximately 60 Gy may be considered in some cases based on risk.

### Regional Nodal Irradiation

The NCCN Guidelines include updated recommendations for regional lymph node irradiation in patients treated with lumpectomy and mastectomy depending on lymph node involvement (see “Principles of Radiation Therapy,” page 337 [BINV-I]).

Two studies, MA.20 and EORTC 22922/10925, evaluated the addition of regional nodal irradiation to the internal mammary nodes and the upper axillary nodes, including the supraclavicular region, in addition to whole breast irradiation or chest wall irradiation after lumpectomy or mastectomy respectively. In MA.20, regional recurrences were reduced from 2.7% with breast irradiation only to 0.7% with the addition of nodal irradiation.<sup>121</sup> The distant recurrences were reduced from 17.3% to 13.4%.<sup>121</sup> An improvement in DFS was seen from 77% to 82% at 10 years in those who received regional nodal irradiation compared with those who did not.<sup>121</sup> In EORTC 22922/10925, regional radiation therapy reduced the incidence of regional recurrences from 4.2% to 2.7% and decreased the rate of distant metastases from 19.6% to 15.9% at a median follow-up of 10.9 years.<sup>122</sup>

### 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.<sup>123</sup> 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 radiation therapy.<sup>124</sup> Patients who may be suitable for APBI are women aged 60 years and 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.<sup>125,126</sup> Follow-up is limited and studies are ongoing.

### Radiation Therapy in Patients Receiving Preoperative Systemic Therapy

The panel recommends that decisions related to administration of radiation therapy for patients receiving preoperative systemic chemotherapy should be made based on maximal stage from prechemotherapy tumor characteristics and/or pathologic stage, irrespective of tumor response to preoperative systemic therapy.

### Rationale for Adjuvant Radiation Recommendations

**Radiation Therapy After Lumpectomy:** After lumpectomy, whole breast irradiation is strongly recommended with or without boost to tumor bed for node-positive disease (category 1 for those with positive nodes; category 2A for those with negative axillary nodes). This recommendation is supported by the results of a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showing reduction in 10-year risk of recurrence in those who received whole breast irradiation versus those who did not (19% vs 35%; relative risk [RR], 0.52; 95% CI, 0.48–0.56).<sup>62</sup> In addition, a significant reduction in 15-year risk of breast cancer death (21% vs 25%; RR, 0.82; 95% CI, 0.75–0.90) was also observed.<sup>62</sup>

**Regional Nodal Irradiation:** The reduction in the risk of locoregional and distant recurrence and improvement in DFS seen in the MA.20 and EORTC 22922/10925 trials supports the importance of regional nodal irradiation after lumpectomy.<sup>121,122</sup> The NCCN panel strongly recommends irradiation of infraclavicular and supraclavicular areas, internal mammary nodes, and any part of the axillary bed that may be suspicious (category 1 for  $\geq 4$  positive nodes). Irradiation of the regional nodal area is generally not recommended by the panel for patients with negative axillary nodes.

If adjuvant chemotherapy is indicated after lumpectomy, radiation should be given after chemotherapy is completed.<sup>127,128</sup> This recommendation is based on results of the “Upfront-Outback” trial in which patients who had undergone breast-conserv-

ing surgery and axillary dissection were randomly assigned to receive chemotherapy after radiation therapy versus 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.<sup>128</sup> However, differences in rates of distant or local recurrence were not statistically significant when the 2 arms were compared at 135-month follow-up.<sup>127</sup>

#### **Radiation Therapy After Lumpectomy in Older Adults:**

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 in which women with clinical stage I, ER-positive breast cancer who were 70 years of age or older at diagnosis were randomized 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 OS, DFS, or need for mastectomy.<sup>129</sup> These results were confirmed in an updated analysis of this study with a median follow-up of 12.6 years.<sup>130</sup> At 10 years, a statistically significant reduction in ipsilateral breast tumor recurrence was seen with radiation therapy, with 98% of patients in the lumpectomy, radiation, and tamoxifen arm free from locoregional recurrence compared with 90% in the lumpectomy and tamoxifen arm.<sup>130</sup> Similar results were obtained in other studies of similar design.<sup>131,132</sup> The determination of whether the difference in tumor control is clinically significant and the patient receives breast radiotherapy should be individualized based on discussion between the patient and her care team.

The NCCN Guidelines allow for the use of lumpectomy (pathologically negative margin required) plus tamoxifen or an aromatase inhibitor without breast irradiation in women aged 70 years or older with clinically negative lymph nodes and ER-positive, T1 breast cancer (category 1).

#### **Radiation Therapy After Mastectomy:**

**Node-Positive Disease:** 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.<sup>133–137</sup> In these trials, the ipsilateral chest wall and the ipsilateral locoregional lymph nodes were irradiated. The results

of EBCTCG meta-analyses<sup>138</sup> 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 therapy was administered.<sup>122</sup> Based on these studies, the current guidelines recommend postmastectomy chest wall irradiation in women with positive ALNs (category 1). Two retrospective analyses have provided evidence for benefit of radiation therapy in only select patients (patients presenting with clinical stage III disease and patients with  $\geq 4$  positive nodes) receiving preoperative systemic therapy before mastectomy.<sup>139,140</sup>

**Regional Nodal Irradiation:** The use of regional nodal irradiation for patients undergoing mastectomy is supported by a subgroup analysis of studies from the Danish Breast Cancer Cooperative Group.<sup>141</sup> In this analysis, a substantial survival benefit was associated with postmastectomy radiation therapy for women with 1 to 3 positive ALNs. In addition, data from the EORTC 22922/10925 trial support the role of regional radiation therapy in this population based on the inclusion of patients who had undergone mastectomy in this study. Based on the previously cited data, the NCCN panel recommends irradiation of infraclavicular and supraclavicular areas, internal mammary nodes and any part of the axillary bed that may be suggestive (category 1 for  $\geq 4$  positive nodes; 2A for 1–3 positive nodes).

**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.<sup>142</sup> Consideration should be given to radiation to the ipsilateral supraclavicular area and to the ipsilateral internal mammary lymph nodes, especially in patients with tumors greater than 5 cm or positive surgical margins. In patients with tumors less than or equal to 5 cm and negative margins but less than or equal to 1 mm, chest wall irradiation should be considered.

In patients with negative nodes, tumor 5 cm or smaller, and clear margins ( $\geq 1$  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 the risk of recurrence in patients with node-negative disease with

high-risk factors such as close margins, tumors 2 cm or larger, premenopausal status, and lymphovascular invasion.<sup>143</sup> Another study showed increased risk of locoregional recurrence in women with node-negative triple-negative breast cancer with tumors 5 cm or smaller.<sup>144</sup>

## 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. Breast reconstruction should not interfere with the appropriate surgical management; this may increase the risk of overall and cancer-related death especially in those with late-stage disease.<sup>145</sup> Coordinating consultation and surgical treatment with a reconstructive surgeon should be executed within a reasonable time frame.

Several reconstructive approaches are summarized for these patients in “Principles of Breast Reconstruction Following Surgery,” pages 335–336 [BINV-H].

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.<sup>146–150</sup> Smoking and obesity are therefore considered relative contraindications to breast reconstruction by the NCCN panel. Smokers and obese patients should be informed of the increased rates of wound healing complications and partial or complete flap failure associated with these risk factors.

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 breast-

feeding, 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 as it relates to cosmetic, body image, and psychosocial issues may be partially overcome through the performance of breast reconstruction with or without reconstruction of the NAC.

Women undergoing mastectomy should be offered consultation regarding options and timing of breast reconstruction.

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.<sup>151–153</sup> 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.<sup>154</sup> 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 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 postmastectomy radiation therapy can impact decisions related to breast reconstruction, because 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.<sup>155,156</sup> Some studies, however, have not found a significant compromise in reconstruction cosmesis after radiation therapy.<sup>157</sup> The preferred approach to breast reconstruction for irradiated patients was a subject of controversy among the panel. Although some experienced breast cancer teams have employed protocols in which immediate tissue reconstructions are followed by radiation therapy, generally radiation therapy is preferred to precede autologous reconstruction due to the reported loss in reconstruction cosmesis (category 2B). When implant reconstruction is planned postmastectomy in a patient requiring radiation therapy, 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.<sup>158</sup> Tissue expansion of irradiated skin can result in a significantly increased risk of capsular contracture, malposition, poor cosmesis, implant exposure, and failed reconstruction.<sup>159,160</sup> 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, 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 after mastectomy, although the impact of this procedure on these quality-of-life issues has not been well-studied.<sup>161–163</sup> Limited data from surgical series with short follow-up 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.<sup>162,164,165</sup> 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 (ie, Nottingham grade 1 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).<sup>166,167</sup> Contraindications for nipple preservation include evidence of nipple involvement, such as Paget's disease or other nipple discharge associated with malignancy, and/or imaging findings suggesting malignant involvement of nipple and subareolar tissues. Several prospective trials are underway to evaluate NAC-sparing mastectomy in the setting of cancer and 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,<sup>168</sup> 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.<sup>169–173</sup> 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 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 before surgery. Oncoplastic techniques for breast conservation can extend breast-conserving surgical options in situations in which the resection by itself would likely yield an unacceptable cosmetic outcome.<sup>174</sup> The evolving field of oncoplastic surgery includes the use of “volume displacement” techniques performed in conjunction with a large partial mastectomy.<sup>175</sup> 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.<sup>175,176</sup>

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.<sup>177</sup>

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, decisions regarding breast reconstruction should primarily focus on treatment of the tumor, and such treatment should not be compromised.

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Individual Disclosures of the NCCN Breast Cancer Panel				
Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Date Completed
Benjamin O. Anderson, MD	None	None	None	2/06/16
Ron Balassanian, MD	None	None	None	12/03/15
Sarah L. Blair, MD	None	None	None	2/24/16
Harold J. Burstein, MD, PhD	None	None	None	9/01/15
Amy Cyr, MD	None	Nanostring	NCCN	11/17/15
Anthony D. Elias, MD	Astellas; CytRx; Eli Lilly and Company; Genentech, Inc.; Immune Design; Incyte; and Medivation	Genentech, Inc.; and SIX1 therapeutics	None	2/25/16
William B. Farrar, MD	None	None	None	2/08/16
Andres Forero, MD	Abbott Laboratories; Abraxis Oncology; Celgene Corporation; Daiichi-Sankyo Co.; Eli Lilly and Company; Genentech, Inc.; GlaxoSmithKline; Incyte; Novartis Pharmaceuticals Corporation; Oncothyreon; Pfizer Inc.; Pharmacyclics; Seattle Genetics; and Synta Pharmaceuticals Corp.	Incyte; and Seattle Genetics	None	2/07/16
Sharon Hermes Giordano, MD, MPH	None	None	None	2/13/16
Matthew Goetz, MD	Eli Lilly and Company	Eli Lilly and Company	None	2/23/16
Lori J. Goldstein, MD	Dompe; Novartis Pharmaceuticals Corporation; and Roche Laboratories, Inc.	None	Novartis Pharmaceuticals Corporation	11/17/15
William J. Gradishar, MD	Genentech, Inc.; and Pfizer Inc.	Eisai Inc.	None	11/10/15
Clifford A. Hudis, MD <sup>a</sup>	Alliance; and I-SPY2	Eli Lilly and Company; Genentech, Inc.; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	None	11/17/15
Steven J. Isakoff, MD, PhD	Abbott Laboratories; Exelixis Inc.; Genentech, Inc.; Merrimack Pharmaceuticals; and Pharmamar	Myriad Genetic Laboratories, Inc.	None	2/23/16
P. Kelly Marcom, MD	Abbott Laboratories; Genentech, Inc.; Novartis Pharmaceuticals Corporation; and Veridex, LLC	None	None	7/17/15
Ingrid A. Mayer, MD	Clovis Oncology; and Novartis Pharmaceuticals Corporation	Novartis Pharmaceuticals Corporation	None	2/04/16
Beryl McCormick, MD	None	None	None	6/01/15
Meena Moran, MD	None	None	None	2/24/16
Sameer A. Patel, MD	None	None	None	4/24/15
Lori J. Pierce, MD <sup>a</sup>	None	None	None	12/09/15
Elizabeth C. Reed, MD	Agendia BV; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	UnitedHealthcare	None	2/23/16
Kilian E. Salerno, MD	None	None	None	2/23/16
Lee S. Schwartzberg, MD <sup>a</sup>	Bayer HealthCare	Bristol-Myers Squibb Company; and Caris Life Sciences	Amgen Inc.; Genentech, Inc.; Helsinn; Merck & Co., Inc.; and Tesaro	9/16/15
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Mary Lou Smith, JD, MBA <sup>a</sup>	None	None	None	2/04/16
Hatem Soliman, MD	Altor; Amgen Inc.; and Genentech, Inc.	Etubics	Celgene Corporation	2/04/16
George Somlo, MD	Abbott Laboratories; and National Cancer Institute	AstraZeneca Pharmaceuticals LP; Celgene Corporation; Millennium Pharmaceuticals, Inc.; and Pfizer Inc.	Celgene Corporation; Millennium Pharmaceuticals, Inc.; and Pfizer Inc.	12/08/15
Melinda Telli, MD	Abbvie; Biomarin Pharmaceuticals; Calithera; Genentech, Inc.; Medivation; Novartis Pharmaceuticals Corporation; OncoSec; PharmaMar; and sanofi-aventis U.S.	Biomarin Pharmaceuticals; and Myriad Genetic Laboratories, Inc.	None	2/18/16
John H. Ward, MD	Galena Biopharma	None	None	11/16/15

<sup>a</sup>The following individuals have disclosed that they have an Employment/ Governing Board, Patent, Equity, or Royalty:

Clifford Hudis, MD: ASCO and Breast Cancer Research Foundation

Lori Pierce, MD: PFS Genomics and UpToDate

Lee Schwartzberg, MD: Caris Life Sciences and GTx

Mary Lou Smith, JD, MBA: Gateway for Cancer Research Foundation, and National Accreditation Program for Breast Centers

<sup>b</sup>The following individuals have disclosed that they have a Spouse/Domestic Partner/Dependent Potential Conflict:

Karen Lisa Smith, MD, MPH: Abbott Laboratories; Abbvie; Express Scripts; Hospira; and Merck & Co., Inc.