Breast Cancer, Version 3.2022

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ABSTRACT

The therapeutic options for patients with noninvasive or invasive breast cancer are complex and varied. These NCCN Clinical Practice Guidelines for Breast Cancer include recommendations for clinical management of patients with carcinoma in situ, invasive breast cancer, Paget disease, phyllodes tumor, inflammatory breast cancer, and management of breast cancer during pregnancy. The content featured in this issue focuses on the recommendations for overall management of ductal carcinoma in situ and the workup and locoregional management of early stage invasive breast cancer. For the full version of the NCCN Guidelines for Breast Cancer, visit NCCN.org.


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 of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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The complete 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 NCCN Breast Cancer Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself. Individual disclosures for the NCCN Breast Cancer Panel members can be found on page 722. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.
Ductal Carcinoma in Situ (DCIS)

The diagnosis of ductal carcinoma in situ (DCIS) has increased since the introduction and increased utilization of screening mammography. According to the American Cancer Society, more than 50,000 cases of DCIS of the female breast will be diagnosed in 2022 in the United States.\(^1\)

**Workup**

The recommended workup and staging of DCIS include history and physical examination; bilateral diagnostic mammography; pathology review; determination of tumor estrogen receptor (ER) status; and MRI, as indicated. For pathology reporting, the NCCN Breast Cancer Panel endorses the College of American Pathologists (CAP) Protocol for both invasive and noninvasive carcinomas of the breast.\(^2\)

The NCCN Panel recommends testing for ER status to determine the benefit of adjuvant endocrine therapy or risk reduction. This is in accordance with the ASCO/CAP guidelines\(^3\) which recommend that ER testing of newly diagnosed DCIS to determine potential benefit of endocrine therapies for breast cancer risk reduction and progesterone receptor (PR) testing be considered optional. Although the tumor HER2 status is of prognostic significance in invasive cancer, its importance in DCIS has not been established. To date, studies have either found unclear or weak evidence of HER2 status as a prognostic indicator in DCIS,\(^4\)–\(^7\) and no statistically significant benefit to the use of trastuzumab concurrent with radiation in HER2 amplified DCIS.\(^8\) The NCCN Panel has concluded that HER2 status for DCIS does not alter the management strategy and therefore is not recommended for DCIS.

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

The role of MRI in management of DCIS remains unclear. MRI has been prospectively shown to have a sensitivity of up to 98% for high-grade DCIS.\(^9\) In a prospective, observational study of 193 patients with pure DCIS who underwent both mammography and MRI imaging preoperatively; 93 (56%) patients were diagnosed by mammography and 153 (92%) were diagnosed by MRI (\(P<.0001\)). Of the 89 patients with high-grade DCIS, 43 (48%) who were not diagnosed by mammography were diagnosed by MRI alone.\(^9\) However, other studies suggest that MRI can overestimate the extent of disease.\(^10\) Therefore, the surgical decisions for performing a mastectomy for DCIS should not be solely

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**Ductal Carcinoma in Situ (DCIS)**

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<thead>
<tr>
<th>DIAGNOSIS</th>
<th>WORKUP</th>
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<tr>
<td>DCIS Tis,N0,M0</td>
<td>History and physical exam; Diagnosisal mammogram; Pathology review; Determination of tumor estrogen receptor (ER) status; Genetic counseling for patients at risk of hereditary breast cancer; Breast MRI as indicated</td>
<td>Breast-conserving surgery (BCS) without lymph node surgery; Total mastectomy with or without sentinel lymph node biopsy (SLNB)(^7) or reconstruction (optional)(^8)</td>
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\(^1\) For risk criteria, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.

\(^2\) See Principles of Dedicated Breast MRI Testing (BINV-I).

\(^3\) The use of MRI has not been shown to increase likelihood of negative margins or decrease conversion to mastectomy. Data to support improved long-term outcomes are lacking.

\(^4\) NCS guidelines\(^5\) may be performed in an effort to obtain negative margins in patients desiring breast-conservation therapy. Patients in whom adequate surgical margins cannot be achieved with BCS should undergo a total mastectomy. For definition of adequate surgical margins, see Margin Status Recommendations After BCS for Invasive Cancers and DCIS (BINV-V).

\(^5\) Complete axillary lymph node dissection should not be performed in the absence of evidence of invasive cancer or proven axillary metastatic disease in patients with apparent pure DCIS. However, a small proportion of patients with apparent pure DCIS will be found to have invasive cancer at the time of their definitive surgical procedure. Therefore, the performance of a sentinel lymph node (SLN) procedure should be considered if the patient with apparent pure DCIS is to be treated with mastectomy or with excision in an anatomic location compromising the performance of a future SLN procedure.

\(^6\) Available online, in these guidelines at NCCN.org. \(^*\) To view the most recent version of these guidelines, visit NCCN.org.

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\(^7\) See Principles of Radiation Therapy (BINV-I).

\(^8\) Patients found to have invasive disease at total mastectomy or re-excision should be managed as having clinical stage 1 or stage II disease (See ST-1*), including lymph node staging.

\(^9\) See Special Considerations to Breast-Conservation Therapy Requiring Radiation Therapy (BINV-D).

\(^10\) WBTR following BCS reduces ipsilateral breast tumor recurrence rates in DCIS by about 50%–75%. Approximately half of the recurrences are invasive and half are DCIS. A number of factors determine local recurrence risk: palpable mass, larger size, higher grade, close or involved margins, and age <50 years. If the patient and physician view the individual risk as “low,” some patients may be treated by excision alone, particularly if they are ER-positive and will be receiving endocrine therapy. Select patients with low-risk DCIS may be considered suitable for APS if they meet all aspects of the definition of low-risk DCIS from the XTOG 9504 trial, including screen-detected DCIS, low to intermediate nuclear grade, tumor size ≤2.5 cm, and surgical resection with margins negative at ≥3 mm.

\(^11\) See Principles of Breast Reconstruction Following Surgery (BINV-I*).
Ductal Carcinoma in Situ (DCIS)

**DCIS POSTSURGICAL TREATMENT**

- Risk reduction therapy for ipsilateral breast following breast-conserving surgery (BCS):
  - Consider endocrine therapy for 5 years for patients with ER-positive DCIS, if:
    - Treated with BCS and RT (category 1), especially for patients with ER-positive DCIS.
    - Treated with excision alone
  - Endocrine therapy:
    - Tamoxifen\(^{10,11}\) or aromatase inhibitor for postmenopausal patients
    - Tamoxifen\(^{10,11}\) or aromatase inhibitor for premenopausal patients with some advantage for aromatase inhibitor therapy in patients <60 years or with concerns for thromboembolism

**SURVEILLANCE/FOLLOW-UP**

- Interval history and physical exam every 6–12 mo for 5 y, then annually
  - Mammogram every 12 mo (first mammogram 6–12 mo, after breast-conservation therapy, category 2B)

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1Available data suggest endocrine therapy provides risk reduction in the ipsilateral breast treated with breast conservation and in the contralateral breast in patients with mastectomy or breast conservation with ER-positive primary tumors. Since a survival advantage has not been demonstrated, individual consideration of risks and benefits is important.

2CYP2D6 genotype testing is not recommended for patients considering tamoxifen.

3The standard dose of tamoxifen is 20 mg/d for 5 years. Low-dose tamoxifen (5 mg/day for 3 years) is an option only if patient is symptomatic on the 20-mg dose or if patient is unwilling or unable to take standard-dose tamoxifen.

Primary Treatment of DCIS

The goal of primary therapy for DCIS is to prevent progression to invasive breast carcinoma. Management strategies for DCIS treatment include surgery (mastectomy or BCS), radiation therapy (RT), followed by adjuvant endocrine therapy in eligible patients to reduce risk of recurrence.

The choice of local treatment does not impact overall disease-related survival; therefore, the individual’s preferences for risk-reduction must be considered.

Several prospective randomized trials of pure DCIS have shown that the addition of whole breast RT (WBRT) after BCS decreases the rate of in-breast disease recurrence,\(^{15–22}\) but not distant metastasis-free survival.\(^{23}\) A meta-analysis of 4 large multicenter randomized trials confirmed the results of the individual trials, demonstrating that the addition of WBRT after BCS for DCIS provides a statistically and clinically significant reduction in ipsilateral breast events (HR [hazard ratio], 0.49; 95% CI; 0.41–0.58, \(P<.00001\)).\(^{24}\) However, these trials did not show that the addition of RT has an overall survival (OS) benefit. The long-term follow-up of the NSABP B-17 showed that at 15 years, RT resulted in a 52% reduction of ipsilateral invasive recurrence compared with excision alone (HR, 0.48; 95% CI, 0.33–0.69; \(P<.0001\)).\(^{21}\) The OS and cumulative all-cause mortality rates through 15 years were similar between the 2 groups (HR for death, 1.08; 95% CI, 0.79–1.48).\(^{21}\) Similar findings were reported by a large observational study of the SEER database that included 108,196 patients with DCIS.\(^{25}\) In a subgroup analysis at 10 years, of
60,000 patients treated with BCS, with or without WBRT, a 50% reduction in the risk of ipsilateral recurrence (adjusted HR, 0.47; 95% CI, 0.42–0.53; P < 0.001) was associated with the addition of WBRT. However, in this study, breast cancer-specific mortality was found to be similar (HR, 0.86; 95% CI, 0.67–1.10; P = 0.22).25

In contrast, several population-based studies suggest beneficial effects of WBRT for DCIS after BCS, for example, the use of WBRT in patients with higher-risk DCIS (eg, higher nuclear grade, younger age, and larger tumor size) was demonstrated to be associated with a modest, but statistically significant improvement in OS.26 In another observational study of the SEER database including 140,366 patients with DCIS, the 15-year breast cancer mortality rate was 1.7% for those treated with breast-conserving therapy (BCT) versus 2.3% for patients treated with BCS alone (HR, 0.77; 95% CI, 0.67–0.88; P <.001), demonstrating a small but significant reduction in breast cancer mortality with BCS and WBRT compared with BCS alone.27

**RT Boost**

The use of RT boost has been demonstrated to provide a small but statistically significant reduction in ipsilateral breast tumor recurrence (IBTR) risk (4% at 20 years) in all age groups for invasive breast cancers.28–31

A pooled analysis of patient-level data from 10 academic institutions evaluated outcomes of pure DCIS patients, all treated with BCS and WBRT (n = 4131) who either received RT boost with a median dose of 14 Gy (n = 2661) or received no boost (n = 1470). The median follow-up of patients was 9 years. A decrease in IBTR was seen in patients who received a boost compared with those who did not at 5 years (97.1% vs 96.3%), 10 years (94.1% vs 92.5%), and 15 years (91.6% vs 88.0%; P = .0389 for all). The use of RT boost was associated with significantly decreased IBTR across the entire cohort of patients (HR, 0.73; 95% CI, 0.57–0.94; P = .01).32 In a multivariate analysis that took into account factors associated with lower IBTR, including grade, ER positive status, use of adjuvant tamoxifen, margin status, and age, the benefit of RT boost still remained statistically significant (HR, 0.69; 95% CI, 0.53–0.91; P <.01).32 Even in patients considered very low risk based on negative margins status (defined as no ink on tumor as per National Surgical Adjuvant Breast and Bowel Project (NSABP) definition, or
Invasive Breast Cancer

LOCOREGIONAL TREATMENT OF cT1-3, cN0 or cN+, M0 DISEASE:

BREAST-CONSERVING SURGERY (BCS) FOLLOWED BY RT

RT AFTER COMPLETION OF BCS AND AXILLARY STAGING

WBRT ± boost to tumor bed, and consider comprehensive regional nodal irradiation (RNI) in patients with central/medial tumors, pT3 tumors, or pT2 tumors with <10 axillary nodes removed and one of the following high-risk features: grade 3, extensive lymphovascular invasion (LVI), or ER-negative.
or

Or Consideration of APBI in selected low-risk patients.\(^3\)\(^,\)\(^4\)
or

Consider omitting breast irradiation in patients ≥70 years of age with ER-positive, cN0, pT1 tumors who receive adjuvant endocrine therapy (category 1).

\(^*\)For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.\(^5\)

\(^1\) Patients with a known or suspected genetic predisposition to breast cancer may have an increased risk of bilateral breast recurrence or contralateral breast cancer with breast-conservation therapy. These patients may be considered for prophylactic bilateral mastectomy for risk reduction. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, ovarian, and pancreatic.\(^6\)

\(^2\) See Considerations for Surgical Axillary Staging (BINV-D).

\(^3\) See Axillary Lymph Node Staging (BINV-E) and Margin Status Recommendations After BCS for Invasive Cancers and DCIS (BINV-F).

\(^4\) Available online, in these guidelines, at NCCN.org. To view the most recent version of these guidelines, visit NCCN.

BCS Alone Without WBRT

RT adds to treatment cost and is accompanied by adverse effects. Therefore, in an attempt to de-escalate treatment and limit morbidity and preserve quality of life (QOL), several trials have examined omission of RT in carefully selected low-risk patients.

There are retrostoscopic series suggesting that selected patients have a low risk of in-breast recurrence when treated with excision alone (without WBRT).\(^35\)\(^,\)\(^36\) For example, in one retrospective review, 10-year disease-free survival (DFS) rates of 186 patients with DCIS treated with BCS alone were 94% for patients with low-risk DCIS and 83% for patients with both intermediate- and high-risk DCIS.\(^35\) In another retrospective study of 215 patients with DCIS treated with BCS without RT, or systemic risk reduction therapy, the recurrence rates over 8 years were 0%, 21.5%, and 32.1% in patients with low-, intermediate- or high-risk DCIS, respectively.\(^36\) The stratification for risk of recurrence in this retrospective study was calculated using the modified Van Nuys Prognostic Index based on tumor grade, size, absence of comedo necrosis, margin width, and age at diagnosis.\(^36\)

A multi-institutional, nonrandomized, prospective study of selected patients with low-risk DCIS treated without radiation has also provided some support for
BCS alone without radiation. Patients were enrolled onto 1 of 2 low-risk cohorts: (1) low- or intermediate-grade DCIS, tumor size 2.5 cm or smaller (n = 561); or (2) high-grade DCIS, tumor size 1 cm or smaller (n = 104). Protocol specifications included excision of the DCIS tumor with a minimum negative margin width of at least 3 mm. Only 30% of the patients received tamoxifen. Of note, margins were substantially wider than the 3-mm protocol requirement in many patients (ie, the low/intermediate-risk patient group margins were $\geq 5$ mm in 62% of patients and $\geq 10$ mm or no tumor on re-excision in 48% of patients). Although the rate of IBTR was acceptably low for the low-/intermediate-grade group at 5 years, at a median follow-up of 12.3 years, the rates of developing an IBTR were 14.4% for low-/intermediate-grade and 24.6% for high grade DCIS ($P = .003$). This suggests that IBTR events may be delayed but not prevented in the seemingly low-risk population.

The RTOG 9804 trial investigated outcomes of RT omission in the setting of low-risk DCIS, randomizing 636 patients with low-risk disease to either RT or observation after surgery. In this study, low risk consisted of low- to intermediate-grade DCIS measuring $< 2.5$ cm, with negative margins of $\geq 3$ mm. With a median follow-up of 7 years, a reduced risk of a local recurrence was seen with use of RT compared with observation (0.9% vs 6.7%; HR 0.11, 95% CI 0.03–0.47). No difference was seen in either DFS or OS. With a follow-up of 15 years, local recurrence rates were reduced by 50% with RT versus without RT (7.1% vs 15.1%; HR, 0.36; 95% CI, 0.20–0.66). The available evidence from 4 randomized trials (NSABP B-39/RTOG 0413, OCGO-RAPID, University of Florence, and GEC-ESTRO) of patients with breast cancer (tumors $\leq 3$ cm) has shown that accelerated partial breast irradiation (APBI) delivered with multicatheter brachytherapy is noninferior in local control compared with WBRT, with similar toxicity and breast cosmetic outcomes. Patients with DCIS constituted 25%, 18%, 8.8%, and 6% of patients in the NSABP B-39/RTOG 0413, OCGO RAPID, University of Florence, and GEC-ESTRO trials, respectively. Per the ASTRO guideline for APBI, patients with screen-detected DCIS measuring $< 2.5$ cm, with grade I or II disease, and with negative margins of 3 mm or more are “suitable” candidates for APBI.

**Margin Status After BCT**

Prospective randomized trials have not been carried out to analyze whether wider margins can replace the need for RT for DCIS. Results from a retrospective study of 445 patients with pure DCIS treated by excision alone
indicated that margin width was the most important independent predictor of local recurrence, although the trend for decreasing local recurrence risk with increasing margin width was most apparent with margins compared with $10\text{ mm}$. In a meta-analysis of 4,660 patients with DCIS treated with BCS and radiation, a surgical margin of $2\text{ mm}$ was associated with increased rates of IBTR compared with margins of $2\text{ mm}$, although no significant differences were observed when margins of $>2\text{ mm}$ to $5\text{ mm}$ or $>5\text{ mm}$ were compared with $2\text{ mm}$-margins.

A study retrospectively reviewed a database of 2,996 patients with DCIS who underwent BCS to investigate the association between margin width and recurrence, controlling all other characteristics. Wider margins were significantly associated with a lower rate of recurrence only in patients who did not receive RT ($P<.0001$), but not in those treated with radiation ($P = .95$).

According to the DCIS Consensus Guideline on Margins by SSO/ASTRO/ASCO, the use of at least a $2\text{ mm}$ margin in DCIS treated with WBRT is associated with low rates of IBTR. Additional factors to consider in assessing adequacy of excision for DCIS include presence of residual calcifications, which margin is close (anterior against skin or posterior against muscle versus medial, superior, inferior or lateral), and life expectancy of the patient. Notably, in situations where DCIS is admixed with invasive carcinoma, the SSO/ASTRO/ASCO Consensus Guideline on Margins for invasive breast cancer should be used, which supports “no tumor on ink” as an adequate margin applying to both the invasive and noninvasive components in this mixed tumor scenario.

**Mastectomy**

Patients with DCIS and evidence of widespread disease (ie, disease involving two or more quadrants) on diagnostic mammography or other imaging, physical examination, or biopsy may require mastectomy.

For DCIS patients undergoing mastectomy, or for local excision in an anatomic location that could compromise the lymphatic drainage pattern to the axilla (eg, tail of the breast), a sentinel lymph node biopsy (SLNB) procedure should strongly be considered at the time of definitive surgery to avoid necessitating a full axillary lymph node (ALN) dissection for evaluation of the axilla. Since only a small proportion of patients (about 25%) with seemingly pure DCIS on initial biopsy will have invasive breast cancer at the time of mastectomy.
Invasive Breast Cancer

OPERABLE DISEASE: BREAST AND AXILLARY EVALUATION PRIOR TO PREOPERATIVE SYSTEMIC THERAPY

Prior to preoperative systemic therapy, perform:
- Core biopsy of breast with placement of image-detectable clips or markers. If not previously performed, should be performed prior to preoperative therapy to demarcate the tumor bed.
- Axillary imaging with ultrasound or MRI (if not previously done) and
- Biopsy + clip placement recommended of suspicious and/or clinically positive axillary lymph nodes, if not previously done.

| Preoperative systemic therapy based on HR and HER2 status* | See Surgical Treatment and Adjuvant Therapy After Preoperative Systemic Therapy (BINV-14) |

the time of the definitive surgical procedure and will ultimately require ALN staging. ALN dissection (ALND) is not recommended unless there is pathologically documented invasive cancer or ALN metastatic disease in patients (by either biopsy or SNLB).

NCCN Recommendations for Primary Treatment of DCIS

Trials are ongoing to determine if there might be a selected favorable biology DCIS subgroup in which surgical excision is not required. Until such time that definitive evidence regarding the safety of this nonsurgical approach is demonstrated, the NCCN Panel continues to recommend surgical excision for all DCIS.

According to the NCCN Panel, primary treatment options for patients with DCIS along with their respective categories of consensus are:

1. BCS plus WBRT with or without boost (category 1).
   While considering RT boost for DCIS, the NCCN Panel recommends an individualized approach based on patient preference and other factors such as longevity. The NCCN Panel notes that WBRT after BCS reduces IBTR recurrence rates in DCIS by about 50%–70%. For DCIS patients treated with BCS alone (without radiation), irrespective of margin width, the risk of IBTR is substantially higher than treatment with excision followed by WBRT (even for predefined low-risk subsets of DCIS patients).

2. Total mastectomy, with or without SLNB with optional reconstruction (category 2A).

3. BCS plus APBI in carefully selected cases (Category 2A). According to the panel, select patients with low-risk DCIS may be considered suitable for APBI if they meet all aspects of the definition of RTOG 9804 low-risk DCIS or ASTRO "suitable" DCIS for APBI.

4. BCS alone (category 2B). The option of BCS alone should be considered only in cases where the patient and the physician view the individual as having a low risk of disease recurrence. For patients with low-risk disease that has been fully resected with negative margins and particularly if they are ER-positive and will be receiving endocrine therapy, the absolute reduction of in-breast recurrence may not be large enough to justify the risks associated with RT. Therefore, according to the NCCN Panel, it may be reasonable to omit RT in such cases.
Contraindications to BCT are listed in the algorithm (see “Special Considerations to Breast-Conserving Therapy Requiring RT,” BINV-G, page 704). Patients treated with mastectomy are appropriate candidates for breast reconstruction (see “Principles of Breast Reconstruction Following Surgery,” BINV-H, available at NCCN.org).

According to the NCCN Panel, complete resection should be documented by analysis of margins and specimen radiography. Postexcision mammography can be considered for any uncertainty about adequacy of the excision remains (eg, the mass and/or microcalcifications are not clearly within the specimen). Clips may be used to delineate the tumor bed and ensure adequate coverage with radiation, provide design of boost and APBI fields, and provide markers should additional surgery be required pending the pathologic margin status review.

For patients with pure DCIS treated by BCS and WBRT, a quantitative description of any tumor close to margin is helpful as a resection width of at least 2 mm is associated with a reduced risk of IBTR relative to narrower negative margin widths. The routine practice of obtaining margins greater than 2 mm to further improve outcomes is not supported by the evidence. When there is only minimal or focal DCIS involvement near the margin, clinical judgment should be used to weigh the risks of re-excision with risk of recurrence for an individual patient.

For patients with DCIS treated with excision alone (no WBRT), regardless of margin width, there is a substantially higher rate of IBTR than treatment with excision and WBRT, even in predefined, low-risk patients. Although the optimal margin width for treatment with excision alone is unknown, it should be at least 2 mm, with some evidence suggesting improved IBTR rates with margin widths wider than 2 mm.

For DCIS with microinvasion (DCIS-M), defined as an invasive focus ≤1 mm in size, the optimal margin width should refer to the DCIS margin definition (≥2 mm), given that the majority of DCIS-M is comprised of DCIS and the natural history and systemic therapy utilization for DCIS-M more closely reflect the treatment pattern for pure DCIS than for invasive carcinoma.

Management of DCIS After Primary Treatment

**Tamoxifen**

DCIS falls between atypical ductal hyperplasia (ADH) and invasive ductal carcinoma within the spectrum of breast proliferative abnormalities. The Breast Cancer Prevention Trial performed by NSABP showed a 75% reduction in the occurrence of invasive breast cancer in...
patients with ADH treated with tamoxifen. These data also showed that tamoxifen led to a substantial reduction in the risk of developing invasive breast disease. The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) overview analysis showed that, with 5 years of tamoxifen therapy, patients with ER-positive or receptor-unknown invasive tumors had a 39% reduction in the annual odds of recurrence of invasive breast cancer.

Similarly, the NSABP B-24 trial found a benefit from tamoxifen for patients with DCIS after treatment with BCS and RT. In that study, patients with DCIS who were treated with BCT were randomized to receive placebo or tamoxifen. At a median follow-up of 13.6 years, patients who received tamoxifen had a 3.4% absolute reduction in ipsilateral in-breast tumor recurrence risk (HR, 0.30; 95% CI, 0.21–0.42; P<.001) and a 3.2% absolute reduction in contralateral breast cancers (HR, 0.68; 95% CI, 0.48–0.95; P=.023). The patients receiving tamoxifen had a 10-year cumulative rate of 4.6% for invasive and 5.6% for noninvasive breast cancers in the ipsilateral breast, compared with 7.3% invasive and 7.2% noninvasive recurrences for those treated with placebo. The cumulative 10-year frequency of invasive and noninvasive breast cancer in the contralateral breast was 6.9% and 4.7% in the placebo and tamoxifen groups, respectively. No differences in OS were noted. A retrospective analysis of ER expression in NSABP B-24 suggests that increased levels of ER expression predict for tamoxifen benefit in terms of risk reduction for ipsilateral and contralateral breast cancer development following BCT.

A phase III trial randomized patients with excised DCIS to receive WBRT or no WBRT and tamoxifen versus no tamoxifen. The randomization was independent for each of the 2 treatments (RT and tamoxifen). With 12.7 years of median follow-up, the use of tamoxifen decreased all new breast events (HR, 0.71; 95% CI, 0.58–0.88; P=.002). The use of tamoxifen decreased ipsilateral and contralateral breast events in the subjects not given WBRT (ipsilateral HR, 0.77; 95% CI, 0.59–0.98; contralateral HR, 0.27; 95% CI, 0.12–0.59), but not in those receiving WBRT (ipsilateral HR, 0.93; 95% CI, 0.50–1.75; P=.80; contralateral HR, 0.99; 95% CI, 0.39–2.49; P=1.0).

The standard dose of tamoxifen is 20 mg/day for 5 years. The phase III TAM-01 trial studied a lower dose of tamoxifen (5 mg for 3 years) in 501 patients with breast intraepithelial neoplasia including DCIS, lobular carcinoma in situ, and ADH. The rate of recurrence of either intraepithelial neoplasia or invasive breast cancer was
5.7% among those receiving tamoxifen 5 mg daily versus 11.9% for those receiving placebo (HR, 0.48; 95% CI, 0.25–0.89) at a median follow up of 5.1 years.\textsuperscript{59} The relative risk (RR) reduction with low dose tamoxifen seen in the TAM-01 trials is consistent with that seen in trials that used a higher dose of tamoxifen, but the rate of severe toxicity compared with placebo was less.

\textbf{Anastrozole}

In patients with ER-positive and/or PR-positive DCIS treated by wide local excision with or without RT, a large, randomized, double-blind, placebo-controlled trial (IBIS-II) compared anastrozole (n=1,471) with tamoxifen (n=1,509). The results demonstrated noninferiority of anastrozole to tamoxifen.\textsuperscript{60} After a median follow-up of 7.2 years, 67 recurrences were reported with anastrozole versus 77 for tamoxifen (HR, 0.89; 95% CI, 0.64–1.23). A total of 33 deaths were recorded for anastrozole and 36 for tamoxifen (HR, 0.9393; 95% CI, 0.58–1.50; \( P = .78 \)).\textsuperscript{60} Although the number of patients reporting any adverse event was similar between anastrozole (n=1,323, 91%) and tamoxifen (n=1,379, 93%); the side-effect profiles of the 2 drugs were different. There were more fractures, musculoskeletal events, hypercholesterolemia, and strokes reported with anastrozole and more muscle spasms, gynecologic cancers and symptoms, vasomotor symptoms, and deep vein thromboses reported with tamoxifen. The NSABP B-35 study randomly assigned 3,104 postmenopausal patients with hormone-positive DCIS treated with lumpectomy and radiation to either tamoxifen or anastrozole for 5 years. Before being randomly assigned, patients were stratified by age—younger or older than age 60. The primary endpoint was breast cancer–free interval.\textsuperscript{61} Anastrozole treatment resulted in an overall statistically significant decrease in breast cancer-free interval events compared with tamoxifen (HR, 0.73; 95% CI, 0.56–0.96; \( P = .0234 \)). The significant difference in breast cancer-free interval between the 2 treatments was apparent in the study only after 5 years of follow-up. The estimated percentage of patients with a 10-year breast cancer–free interval was 89.1% in the tamoxifen group and 93.1% in the anastrozole group.\textsuperscript{61} In addition, anastrozole resulted in further improvement in breast cancer-free interval, in younger postmenopausal patients (<60 years old). With respect to adverse effects, the overall incidence of thrombosis or embolism was higher in the tamoxifen group while the anastrozole group had slightly more cases of arthralgia and myalgia.\textsuperscript{61}

Results of the IBIS-II and the NSABP-B-35 studies indicate that anastrozole provides at least a comparable
Invasive Breast Cancer

MARGIN STATUS RECOMMENDATIONS AFTER BREAST-CONSERVING SURGERY (BCS) FOR INVASIVE CANCERS AND DCIS

- Margins should be evaluated on all surgical specimens from breast-conserving surgery (BCS). 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.
- For mammographically detected DCIS with microcalcifications, complete resection should be documented by analysis of margins and specimen radiography. Post-excision mammography can be considered if there is uncertainty.
- The NCCN Panel accepts the definitions of negative margins after breast-conservation therapy from the 2014 SSO/ASTRO Margin Guideline1 for Stage III Invasive Cancers and the 2016 SSO/ASTRO/ASCO Guideline for DCIS.2 For patients with stage I or II invasive cancers after BCS, a positive margin is defined as “ink on tumor” (any invasive cancer or DCIS cells on ink). These patients generally require further surgery—either a re-excision to achieve a negative margin or a mastectomy. If re-excision is technically feasible to allow for BCS to achieve “no ink on tumor,” 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. There may be select patients with stage III invasive cancers who may be eligible for BCS. For these patients, the margins status would be accessed with similar definitions.

DCIS

- For patients with pure DCIS treated by BCS and WBRT, a quantitative description of any tumor close to margin resection width of at least 2 mm is associated with a reduced risk of ipsilateral breast tumor recurrence (IBTR) relative to narrower negative margins widths, while the routine practice of obtaining margins greater than 2 mm to further improve outcomes is not supported by the evidence. When there is only minimal or focal DCIS involvement near the margin, clinical judgment should be utilized to weigh the risks of re-excision with risk of recurrence for an individual patient.
- For patients with DCIS treated with excision alone (no WBRT), regardless of margin width, there is a substantially higher rate of IBTR than treatment with excision and WBRT, even in predefined, low-risk patients. Although the optimal margin width for treatment with excision alone is unknown, it should be at least 2 mm, with some evidence suggesting improved IBTR rates with margin widths wider than 2 mm.
- DCIS with microinvasion (DCIS-M), defined as an invasive focus ≤5 mm in size, should refer to the DCIS margin definition when considering the optimal margin width (>2 mm), given that the majority of DCIS-M is comprised of DCIS and systemic therapy utilization for this lesion more closely reflects the treatment pattern for DCIS than for invasive carcinoma.

NCCN Recommendations for Management of DCIS After Primary Treatment

According to the NCCN Panel, in patients with ER-positive DCIS treated with BCT, endocrine therapy with tamoxifen (for premenopausal and postmenopausal patients) or an aromatase inhibitor (for postmenopausal patients, especially those <60 years of age or in those with concerns of embolism), may be considered as a strategy to reduce the risk of ipsilateral breast cancer recurrence (category 1 for those undergoing BCT followed by RT; category 2A for those undergoing excision alone). The benefit of endocrine therapy for ER-negative DCIS is not known. Low-dose tamoxifen (5 mg/day for 3 years) is an option only if the 20-mg standard dose of tamoxifen is not tolerated (see DCIS-2, Page 693).

Follow-up of patients with DCIS include interval history and physical examination every 6 to 12 months for 5 years and then annually, as well as yearly diagnostic mammography. In patients treated with BCT, the first follow-up mammogram should be performed 6 to 12 months after the completion of RT (category 2B; see DCIS-2). Patients receiving endocrine therapy for risk reduction should be monitored as described in the NCCN Guidelines for Breast Cancer Risk Reduction (available at NCCN.org).

Invasive Breast Cancer

Workup for Nonmetastatic (M0) Invasive Breast Cancer

The recommended workup of localized invasive breast cancer (listed on BINV-1, page 694) includes a history and physical exam. Complete blood count (CBC) and liver function tests (LFTs) have no added benefit in the detection of underlying metastatic disease in asymptomatic patients with early-stage breast cancer.62 In addition,
monitoring of disease relapse with any tumor markers is not recommended.

Imaging

Imaging with bilateral diagnostic mammography is recommended; breast ultrasonography is recommended only if necessary. The use of MRI in the workup remains controversial. 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 including MRI-guided biopsy in many circumstances. MRI findings tend to overestimate extent of disease, resulting in increased frequency of mastectomies.

MRI findings alone are not sufficient to determine whether BCT is optimal as additional tissue sampling is needed to verify true malignant disease warranting excision. MRI use may increase mastectomy rates by identifying areas of mammographically occult disease that may have been adequately treated with radiation after BCS had the disease remained undiscovered without MRI.

Two prospective randomized studies have examined the utility of preoperative MRI in determining disease extent, and neither demonstrated improvement in rates of re-excision after initial BCS. Retrospective review of the utility of MRI showed conflicting outcome results—one with benefit and another without. One systematic review documented that breast MRI staging altered surgical treatment in 7.8%–33.3% of patients, however, no differences in local recurrence or survival have been demonstrated. In addition, there is no evidence that use of breast MRI increases rates of margin-negative resection.

Breast MRI may assist with identification and management of clinically occult primary tumors presenting with axillary nodal metastases. In patients with Paget disease not identifiable on mammography, breast MRI may help determine the extent of disease. Breast MRI also has utility in screening patients with higher than average-risk based on family history.

If breast MRI imaging is performed, a dedicated breast coil, an imaging team experienced with reading breast MRI and performing MRI-guided biopsy, and multidisciplinary management are the standard of care.

According to the NCCN Panel, the use of MRI is optional and is not universally recommended by experts.
in the field. Breast MRI may be used for staging evaluation to define extent of cancer, in the adjuvant or neoadjuvant setting, to detect the presence of multifocal or multicentric cancer in the ipsilateral breast, or as screening of the contralateral breast cancer at time of initial diagnosis. Additional indications for breast MRI include clinical axillary metastasis with an occult primary cancer; Paget disease of the nipple with breast primary not identified by other breast imaging modalities or physical examination, follow-up screening of patients with prior mammographically-undetected breast cancers; and those whose lifetime risk of a second primary breast cancer is >20% (based on models largely dependent on family history).

Pathology Assessment
Full knowledge of extent of disease and biologic features is central to the treatment of breast cancer. The NCCN Breast Cancer Panel endorses the use of the CAP protocols for reporting the pathologic analysis of all breast cancer specimens. Data from both national and local surveys show that as many as 50% of breast cancer pathology reports are missing some elements critical to patient management. Significant omissions include failure to orient and report surgical margins and failure to report tumor grade consistently. The specimens should be oriented for the pathologist, and specific requests for determination of biomarkers should be stated (e.g., ER, PR, and HER2 status). The panel also recommends testing for Ki-67, if hormone receptor-positive, HER2-negative and considering adjuvant abemaciclib.

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

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 patients have higher rates of psychosocial distress than patients diagnosed at older ages. The NCCN Breast Cancer Panel recommends assessing for distress in patients newly diagnosed with breast cancer using guidance from the NCCN Guidelines for Distress Management (available at NCCN.org).
Invasive Breast Cancer

PRINCIPLES OF RADIATION THERAPY

Optimizing Delivery of Individual Therapy
- It is important to individualize RT planning and delivery.
- 3-D CT-based treatment planning should be routinely utilized to delineate target volumes and adjacent organs at risk.
- Radiation to the breast/chest wall and nodal regions is generally delivered with single energy or mixed energy photons ± electrons.
- Improved homogeneity of the target dose and sparing of normal tissues can be accomplished using compensators such as wedges, forward planning using segments, and intensity-modulated RT (IMRT).
- Additional techniques such as respiratory control (deep inspiration breath-hold), prone positioning, and cardiac blocks may also be used to try to further reduce dose to heart, lung, and adjacent normal tissue.
- Verification of treatment setup consistency is done with weekly imaging. When using certain techniques (ie, prone breast), more frequent imaging may be appropriate. Standard utilization of daily imaging is not recommended.
- When treating the internal mammary nodes, dose-volume histograms (DVHs) should be used to evaluate dose constraints, dose to normal tissues (ie, heart, lung), and planning target volumes (PTVs).
- It is common for RT to follow chemotherapy when chemotherapy is indicated.

Whole Breast Radiation
- Target definition is the breast tissue at risk.
- RT dosing:
  - The whole breast should receive a hypofractionated dose of 40–42.5 Gy in 15–16 fractions; in selected cases 45–50.4 Gy in 25–28 fractions may be considered.
  - 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.
  - Lumpectomy cavity boost can be delivered using enface electrons, photons, or brachytherapy.
  - Ultra-hypofractionated WBRT of 28.5 Gy delivered as 5 (once-a-week) fractions may be considered in select patients aged >50 years following BCS with pT1b/T2a/N0, though the optimal fractionation for the boost delivery is unknown for this regimen.8,26
  - 3-D planning to minimize inhomogeneity and exposure to heart and lung is essential when using this regimen.

Fertility and Sexual Health

The general considerations for fertility and sexual health/ function outlined for specific populations in NCCN Guidelines for Adolescent and Young Adult Oncology and NCCN Guidelines for Survivorship (both available at NCCN.org) are applicable to all patients diagnosed with breast cancer. The panel recommends referring to those guidelines for guidance.

Numerous epidemiologic studies have shown that childbearing after treatment of invasive breast cancer does not increase rates of recurrence or death from breast cancer.88 The offspring of pregnancies after treatment of breast cancer do not have an increased rate of birth defects or other serious childhood illness. However, treatment of breast cancer, especially with cytotoxic agents, may impair fertility and fertility may wane during the 5 to 10 years of adjuvant endocrine therapy.

While the potential to regain menstrual function within 2 years of completing chemotherapy is possible, especially for those younger than age 35,88 resumption of menses does not correlate with fertility, and conversely, fertility may be preserved without menses. Therefore, all premenopausal patients should be informed about the potential impact of chemotherapy on fertility and offered the option of fertility preservation if future childbearing is desired.

Considerations for fertility preservation should incorporate 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, as well as the timing and duration allowed for fertility preservation.

Several studies report lower rates of fertility discussion among female patients with cancer90–92 despite the updated ASCO guidelines stating that patients should not be excluded from consideration for discussion of fertility preservation for any reason, including parity, prognosis, age, and socioeconomic status.93 The NCCN Panel recommends that all treating physicians should have a discussion with their patients of childbearing potential regarding the options for fertility preservation. Patients who desire to bear children after systemic therapy should be referred to a fertility specialist prior to initiating systemic (chemotherapy or endocrine) therapy.93–99

Randomized trials have demonstrated that GnRH agonists (such as goserelin) administered prior to initiating chemotherapy and then administered concurrently with adjuvant chemotherapy protect against ovarian failure and reduce the risk of early menopause.100–102 In one trial goserelin improved the probability of pregnancy from 11% to 21% in patients with HR-negative early-stage breast cancer.
Breast Cancer. Smaller historical experiences in patients with HR-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 specifics of fertility preservation options including hormonal interventions, ovarian stimulation, embryo or oocyte cryopreservation, and other investigational options, as well as the probability of successful gestation and childbirth.

Combining the various modalities for a specific patient may increase the odds of preservation of future fertility. It is important for fetal safety that patients actively avoid becoming pregnant during breast cancer treatment.

Additional Diagnostic 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. Recommendations for additional metastatic workup should be performed for those patients with signs or symptoms suspicious for metastatic disease, based on lack of evidence to demonstrate any benefits with metastatic workup in early-stage disease. 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. For patients with stage III breast cancer, the prevalence of a positive liver ultrasound and positive chest X-ray was 6% and 7%, respectively.

CBC, comprehensive metabolic panel, liver function and alkaline phosphatase tests should be considered only if the patient is a candidate for preoperative or adjuvant systemic therapy (BINV-12, page 697). A bone scan or sodium fluoride PET/CT is indicated in patients presenting with localized bone pain or elevated alkaline phosphatase. Bone scan or sodium fluoride PET/CT may not be needed if FDG PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component.

A diagnostic chest CT is indicated only if pulmonary symptoms (ie, cough or hemoptysis) are present. Likewise, abdominal and pelvic imaging using diagnostic CT or MRI
Invasive Breast Cancer

PRINCIPLES OF RADIATION THERAPY

- Studies of APBI suggest that rates of local control in selected low-risk patients with early-stage breast cancer are comparable to those treated with standard WBRT. However, compared to standard WBRT, several studies document an inferior cosmetic outcome with external beam delivery methods of APBI. Follow-up is limited and studies are ongoing.
- Patients are encouraged to participate in clinical trials.
- The NCCN Panel recommends APBI for any patient who is BRCA negative and meets the 2016 ASTRO criteria.
- The 2016 ASTRO criteria defines patients age ≥50 years to be considered “suitable” for APBI if:
  - Invasive ductal carcinoma measuring ≤2 cm (pT1 disease) with negative margin widths of ≤2 mm, no LVI, and ER-positive or
  - Low/intermediate nuclear grade, screening-detected DCIS measuring ≤2.5 cm with negative margin widths of ≥3 mm.
- RT dosing:

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<th>Regimen</th>
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* The protocol mandated MRT.

is indicated if the patient has elevated alkaline phosphatase, abnormal results on LFTs, abdominal symptoms, or abnormal physical examination of the abdomen or pelvis.

FDG PET/CT may be performed at the same time as diagnostic CT, and may be helpful in situations where standard staging studies are equivocal or suspicious. FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases when used in addition to standard staging studies. The routine use of FDG PET/CT scanning is not recommended in the staging of clinical stage I, II, or operable III (T3 N1) breast cancer, due to its high false-negative rate for the detection of lesions that are small (<1 cm) and/or low grade disease, the high rate of false-positive scans in patients without locally advanced disease, the low sensitivity for detection of axillary nodal metastases, and the low probability of these patients having detectable metastatic disease.

Overall Locoregional Treatment of cT1–3, cN0 or cN+, M0 Disease

Surgery

Patients with early-stage operable breast cancer initially undergo upfront definitive surgery (BCS or mastectomy), and adjuvant systemic therapy, if indicated, based on primary tumor characteristics, such as tumor size, grade, lymph node involvement, ER/PR status, expression of HER2- receptor, and tumor genomics. Some patients with early-stage operable HER2-positive or triple-negative disease may be treated with preoperative systemic therapy first, followed by surgery. For NCCN Panel recommendations and consideration for preoperative systemic therapy, refer to NCCN.org. Radiation is typically sequenced after definitive surgery and after systemic chemotherapy (if delivered).

Several randomized trials document that mastectomy is equivalent to BCT which includes BCS with WBRT with respect to OS as primary treatment of the majority of patients with stage I and stage II breast cancers (category 1). The optimal choice of surgery is based on a shared decision made by the patient and clinician after discussing benefits and risks of mastectomy versus BCT in regards to long-term survival, risk of local recurrence, and the impact on cosmetic outcome and overall quality of life.

Breast Conserving Surgery

BCS allows patients to preserve their breast without sacrificing oncologic outcome. BCS is contraindicated for patients who are pregnant and would require radiation
dure over BCS.

Mastectomy is indicated for patients who are not candidates for lumpectomy (category 2B). Relative contraindications to lumpectomy include previous RT to the breast or chest wall; active connective tissue disease involving the skin (especially scleroderma and lupus); persistently positive pathologic margin; or in those with a known or suspected genetic predisposition to breast cancer who may have an increased risk of ipsilateral breast recurrence or contralateral breast cancer with BCT or who may be considered for prophylactic bilateral mastectomy for risk reduction as per the criteria in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (available at NCCN.org) or may have known or suspected Li-Fraumeni syndrome (category 2B).

Several studies of patients with early-stage breast cancer treated with BCS have identified young age as a significant predictor of an increased likelihood of IBTRs after BCT.118-120 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 patients with breast cancer, thereby confounding the independent contributions of age and treatment to clinical outcome.121

With respect to OS outcomes for young patients with breast cancer, BCT or mastectomy are similar.115,116,122-124 Some studies have shown improved survival125-127 and fewer postsurgical complications128 with BCS.

**Mastectomy**

Mastectomy is indicated for patients who are not candidates for BCS or those who choose to undergo this procedure over BCS.

Only limited data are available on the survival impact of risk-reducing contralateral mastectomy in patients with a unilateral breast cancer.129 Analysis of patients included in the SEER database treated with mastectomy for a unilateral breast cancer from 1998 to 2003 showed that contralateral risk reducing 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 patients (18–49 years of age) with stage I/II, ER-negative breast cancer (HR, 0.68; 95% CI, 0.53–0.88; P=.004).130 The 5-year breast cancer survival for this group was only slightly improved with contralateral risk reducing mastectomy versus without (88.5% vs 83.7%, difference = 4.8%).130 These differences observed in retrospective analysis could be due to selection bias among patients who chose risk reducing contralateral mastectomy.131 A statistical simulation of survival outcomes after risk reducing contralateral mastectomy among patients 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.130 Data from another meta-analysis found no absolute reduction in risk of distant metastases with risk-reducing mastectomy.133 Furthermore, among patients with unilateral breast cancer who have an increased familial/genetic risk, a decrease in metastatic contralateral breast cancer incidence was observed in those who received risk-reducing contralateral mastectomy, although no improvement was seen in OS of these patients.133

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

The NCCN Panel recommends referring to the NCCN Guidelines for Older Adult Oncology (at NCCN.org) for special considerations for this population.

**Margin Assessment**

After surgical resection, a careful histologic assessment of resection margins is essential. The NCCN Panel notes that benefit of BCS is predicated on achieving pathologically negative margins after resection. The NCCN Panel accepts the most recent definition outlined in the guidelines established by SSO/ASTRO as the standard for negative surgical margins for invasive cancer.134

For patients with stage I or II invasive cancers after BCS, a positive margin is defined as “ink on tumor” (any invasive cancer or DCIS cells on ink). Patients with positive margins generally require further surgery—either a re-excision to achieve a negative margin or a mastectomy. If re-excision is technically feasible to achieve “no ink on tumor,” 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. There may be select patients with stage III invasive cancers who may be eligible for BCS. For these patients, the margin status would be assessed with similar definitions. If margins remain positive after further surgical re-excision(s), then mastectomy may be required for optimal local disease control.

To adequately assess margins following surgery, the panel recommends that the surgical specimens be directionally oriented and that the pathologist provide descriptions of the gross and microscopic margin status and the distance, orientation, and type of tumor (invasive cancer or pure DCIS) in relation to the closest margin. Marking the tumor bed with clips facilitates accurate planning of the radiation boost field, where appropriate.

For invasive breast cancers that have a component of DCIS, the negative margin definition of “no ink on tumor” should be used based on the SSO/ASTRO Consensus Guideline on Margins unless it is DCIS with microinvasion, which behaves more like pure DCIS and 2-mm margins should be used based on the SSO/ASTRO Consensus to identify residual calcification.

The same margin recommendations cannot be applied directly to patients undergoing APBI, where data regarding local recurrence are more limited than WBRT. Individualized clinical judgment should be used on a case-by-case basis, using postoperative mammography to identify residual calcifications and clinical-pathologic factors such as quantitative extent of disease near margin, presence of extensive intraductal component, young age, or multiple close margins to assist in identifying patients who may have an increased risk of ipsilateral recurrence and therefore may benefit from re-excision.

Surgical Axillary Staging

Axillary status is important for planning systemic adjuvant treatment and RT. The lymphatic pathways from the breast go to the ALNs, internal mammary, infraclavicular, and/or supraclavicular lymph nodes.

Traditional level I and level II ALNDs require that at least 10 lymph nodes be provided for pathologic evaluation to accurately stage the axilla. ALND should be extended to include level III nodes only if gross disease is apparent in the level II and I 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 and II; BINV-E, page 702).

Historically, ALND has been the standard of care for axillary staging. However, ALND is associated with lymphedema and other significant morbidities. This has been largely replaced with SLNB.

SLN mapping injections may be peritumoral, subareolar, or subdermal. 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 treatment decisions should be made based solely on H&E staining. This recommendation is further supported by a randomized clinical trial (ACOSOG Z0010) for patients with H&E negative nodes where further examination by cytokeratin IHC was not associated with improved OS over a median of 6.3 years. In the uncommon situation in which H&E staining is equivocal, reliance on the results of cytokeratin IHC is appropriate.

Two randomized trials compared SLNB alone versus ALND. The Milan trial (1998–1999) randomized 516 patients treated with BCS with tumors up to 2 cm to 2 arms, one receiving immediate axillary dissection and the other receiving the dissection only if the sentinel node was involved. After 79 months follow up, there was no difference in OS and DFS. Another similar study, (NSABP) B-32, conducted between 1999 and 2004, randomized 5,611 patients with invasive breast cancer up to 2 cm to either ALND or SLNB alone with ALND performed only if the SLN was positive. After 95.6 months of follow up, OS and DFS were similar in the 2 groups. Results of a subgroup analysis of this study showed patients with ALND had significantly higher arm morbidity and significantly more restricted work and social activity and impaired QOL.

The ALMANAC trial studied the QOL in patients with SLNB versus ALND in 1,031 patients. After 12 months, lymphedema and sensory loss were higher in the ALND group. Operative time, drainage use, hospitalization, and resumption of normal life were much longer in ALND compared with the SLNB group. The SNAC trial and the DBCCG trial also showed less morbidity with SLNB compared with ALND.

Based on the results of these studies, it was clarified that for negative sentinel nodes, ALND is not needed. The ACOSOG Z0011 trial addressed the role of ALND in those with a clinically negative axilla but pathologically positive lymph nodes from an SLNB. This trial randomized patients greater than or equal to 18 years of age with clinical T1/T2 tumors, fewer than 3 positive SLNs, undergoing BCS and WBRT, to SLNB alone (n=436) or to a
completion ALND (n=420). In this study, there was no difference in local recurrence, DFS, or OS between patients with positive SLN undergoing a completion ALND versus no ALND. Only ER-negative status, age less than 50, and lack of adjuvant systemic therapy were associated with decreased OS.\textsuperscript{150} At a median follow-up of 6.3 years, locoregional recurrences were noted in 4.1% of patients in the ALND group and 2.8% of patients in the SLNB group (P=.11). Median OS was approximately 92% in each group.\textsuperscript{151} Long term follow-up (median 9.25 years) results of the ACOSOG Z0011 study showed no statistically significant difference in local recurrence-free survival between trial arms (P=.13).\textsuperscript{152} The cumulative incidence of ipsilateral axillary recurrences at 10 years was 0.5% (2 patients) in those who underwent ALND and 1.5% (5 patients) in those who underwent SLNB-alone (P=.28).\textsuperscript{152} The 10-year cumulative incidence of locoregional recurrences was 6.2% with ALND and 5.3% with SLNB alone (P=.36).\textsuperscript{152}

The results of the ACOSOG Z0011 trial demonstrate that there is no benefit to ALND in patients with early-stage breast cancer who have only one or two SLN metastases (minimal nodal burden) on SLNB after receiving WBRT as part of BCT. Mastectomy patients were not enrolled in the ACOSOG Z0011 trial since these patients do not routinely receive radiation. Another randomized trial (IBCSG 23-01) was specifically designed to compare outcomes in patients with sentinel micrometastases (≤2 mm) treated with ALND versus no ALND.\textsuperscript{153} While the ACOSOG Z0011 trial was limited to those undergoing BCT, this trial included patients undergoing mastectomy (9%).\textsuperscript{153} Between the group treated with SLNB plus ALND versus the group that had SLNB alone, there were no differences in 5 year DFS (84.4%; 95% CI 80.7%–88.1% vs 87.8%; 95% CI 84.4%–91.2%), cumulative incidence of breast cancer events - including local, regional, contralateral breast, and distant recurrence (10.8%; 95% CI, 7.6–14.0 vs 10.6%; 95% CI, 7.5–13.8) or OS (97.6%; 95% CI, 96.0%–99.2% vs 97.5%; 95% CI, 95.8%–99.1%).\textsuperscript{153} Regional recurrence was less than 1% for those who underwent ALND and 1% for those who did not undergo ALND.\textsuperscript{153} The results of this trial show that in patients with micrometastases on SLNB, ALND is not needed.

The results of a trial by the European EORTC group (AMAROS) assessed whether axillary RT provides regional disease prior to preoperative systemic therapy, SLNB has a >10% false-negative rate when performed after preoperative systemic therapy. In the SENTINA study,\textsuperscript{157} the overall false negative rate was 14.2%. In the ACOSOG-Z1071 trial,\textsuperscript{158} the false negative rate was 12.6% and in the SN FNAC trial,\textsuperscript{159} the false negative rate was 13.3%.

Subgroup analyses from studies have shown that (1) using dual-agent lymphatic mapping (radiotracer and blue dye), (2) identifying 3 or more SLNs, and (3) marking the metastatic lymph node with a clip before neoadjuvant therapy and then resecting it at the time of surgery reduces false-negative rates to <10%.

A subgroup analysis of the ACOSOG Z1071 trial showed lower false negative rates in patients who had a clip placed in the positive lymph nodes at the time of initial biopsy followed by removal of the clipped node during SLN surgery after preoperative systemic therapy.\textsuperscript{160} A another study of selective localization and removal of clipped nodes with SLN biopsy, known as “targeted axillary dissection,” showed false-negative rates reduced to approximately 2% compared with 4% with removal of the clipped lymph node alone.\textsuperscript{161}

Several ongoing clinical trials are examining further de-escalation of axillary surgery in those who have positive nodes after preoperative systemic treatment.
The Alliance A011202/MAC19 trial (ClinicalTrial.gov identifier: NCT01901094) study is randomly assigning patients who have sentinel node–positive disease after neoadjuvant chemotherapy to ALND versus no further axillary surgery. Both arms will receive regional nodal radiation. The SLNB alone arm will include axillary RT to the undissected axilla (levels I–III) whereas the ALND arm will not include RT to levels I or II axillae.

**NCCN Recommendations for Surgical Axillary Staging**

If ALNs are clinically negative (no palpable nodes) at the time of diagnosis or ≤2 suspicious lymph nodes are found on imaging or ≤2 positive lymph nodes confirmed by needle biopsy, the panel recommends SLN mapping.

If SLN is negative, no further surgery is needed in these patients. If SLN is positive, based on the ACOSOG Z0011 data, no further surgery is recommended only if all of the following criteria are met: the patients have cT1-2, N0 tumors, have not received neoadjuvant systemic therapy, have 1 or 2 positive SLNs, and will undergo BCT (BCS + WBRT). If any of these criteria are not met, the panel recommends level I and II axillary dissection.

Based on the AMAROS and OTASAR trial data, no further surgery is recommended only if all of the following criteria are met: the patients have cT1-2, N0 tumors, have not received neoadjuvant systemic therapy, have 1 to 2 positive SLNs, and will undergo mastectomy along with adjuvant RT with intentional inclusion of undissected axilla at risk. If any of these criteria are not met, the panel recommends level I and II axillary dissection. In select patients undergoing mastectomy with clinically negative axillae but 1 or 2 positive SLNs, the panel notes that axillary radiation may replace ALND for regional control of disease. Based on the results of the IBCSG 23-01 trial, the NCCN Panel recommends no ALND for patients with positive SLNs when that disease is limited to only micrometastatic. According to the AJCC staging, micrometastatic nodal involvement is defined as a metastatic deposit >0.2 mm but ≤2.0 mm.

In patients with clinically suspicious (palpable) lymph nodes or 3 or more suspicious lymph nodes on imaging, or if preoperative systemic therapy is being considered for patients with suspicious lymph nodes at diagnosis on exam or imaging, the panel recommends pathologic confirmation of malignancy using ultrasound-guided fine-needle aspiration or core biopsy of suspicious nodes with clip placement.

According to the NCCN Panel, the recommendation for ALND of level I and II nodes is limited to patients with biopsy proven axillary metastases (in those who did not receive neoadjuvant systemic therapy) or who have residual disease after preoperative chemotherapy. Highly selected patients with biopsy proven axillary metastases, who then converted to clinically node negative after preoperative systemic therapy, may undergo SLNB with removal of the clipped lymph node. This is a currently a category 2B recommendation as the rate of false negatives is high when SLN is performed after preoperative systemic therapy.

According to the NCCN Panel, based on available data, the false negative rate can be reduced by marking biopsied lymph nodes to document their removal, using dual tracer, and by removing ≥3 sentinel nodes (targeted ALND). When sentinel nodes are not successfully identified, the panel recommends level I and II axillary dissection be performed for axillary staging.

**Radiation Therapy**

**Principles of RT**

It is important to individualize RT 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 RT (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, particularly the heart and lung. Verification of treatment setup consistency is done with weekly imaging. When using certain techniques (ie, prone breast), more frequent imaging may be appropriate. Standard utilization of daily imaging is not recommended. Radiation to the breast/chest wall and nodal regions is generally delivered with single energy or mixed energy photons with or without electrons. Dose-volume histograms should be used to evaluate dose constraints, evaluate dose to normal tissues (ie, heart, lung), and ensure adequate coverage to the intended planning target volumes, including the breast/chest wall, supraclavicular fossa, axillary levels I–III and internal mammary nodes.

**Whole Breast Radiation Therapy**

WBRT reduces the risk of local recurrence and has shown to have a beneficial effect on survival. Randomized trials have demonstrated decreased in-breast recurrences with an additional boost dose of radiation (by photons, brachytherapy, or electron beam) to the tumor bed. For greater homogeneity of target dose and to spare normal tissues using compensators such as tissue wedges, forward planning using segments, and IMRT may be used.

Four randomized clinical trials have investigated hypofractionated WBRT 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. The 10-year follow-up data...
from the START trials\textsuperscript{173} are consistent with the 10-year results of the Canadian trial,\textsuperscript{172} 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 the standard dose of 50 Gy in 25 fractions over 5 weeks.\textsuperscript{172} 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 regimen.\textsuperscript{173}

Another randomized trial showed similar outcomes among patients receiving a hypofractionated schedule (40 Gy in 15 fractions) compared with standard fractionation (50 Gy in 25 fractions), in patients (n=1,854) with node-negative breast cancer (n=1,608) or DCIS (n=246).\textsuperscript{174} The 9-year risk of locoregional recurrence was 3.3\% in the 50-Gy group and 3.0\% in the 40-Gy group. The 9-year OS was 93.4\% in the 50-Gy group and 93.4\% in the 40-Gy group. Radiation-associated cardiac and lung disease were comparable between the groups.

Other shorter schedules of delivering WBRT have also been studied with similar results. The FAST trial, compared patients 50 years of age and older with low-risk invasive breast carcinoma (pT1-2 pN0) randomly assigned to the standard schedule of 50 Gy in 25 fractions over 5 weeks or 30 Gy or 28.5 Gy in 5 fractions once-weekly. After 10-year follow-up, there were no significant differences reported in normal tissue effects for the standard 50 Gy in 25 fractions schedule versus a once-weekly schedule for 5 weeks totaling 28.5 Gy, but normal tissue effects were higher with a weekly schedule for 5 weeks totaling 30 Gy.\textsuperscript{175}

The FAST Forward trial randomized patients with non-metastatic breast cancer (n=4,096) after BCS or mastectomy, to one of the following: 40 Gy in 15 fractions over 3 weeks, or 27 Gy in 5 fractions over 1 week, or 26 Gy in 5 fractions over 1 week to either whole breast or chest wall.\textsuperscript{176} The 5-year incidence of ipsilateral breast tumor relapse was 2.1\% with the standard 40 Gy in 15 fractions over 3 weeks versus 1.7\% with 27 Gy in 5 fractions over 1 week (5.4 Gy per fraction; HR, 0.86; 95\% CI, 0.51–1.44) and 1.4\% with 26 Gy in 5 fractions over 1 week (5.2 Gy per fraction; HR, 0.67; 95\% CI, 0.38–1.16).\textsuperscript{176} The moderate or marked tissue effects in the breast or chest wall were 15\% with 27 Gy, 12\% with 26 Gy, and 10\% with 40 Gy, but differences between the 40 Gy and 26 Gy groups were not statistically different.\textsuperscript{176}

**RT Boost to Tumor Bed**

In patients with higher risk characteristics (such as age <50 years, high-grade disease, or patients with focally positive margins), an RT boost has been shown to reduce local relapse.\textsuperscript{28,30,166,173,177–179} RT boost treatment in the setting of breast conservation can be delivered using enface electrons, photons, or brachytherapy.\textsuperscript{180}

**NCCN Recommendations for WBRT**

The panel has defined the target as breast tissue at risk. The NCCN Panel recommends a dose of 40–42.5 Gy in 15–16 fractions for all patients getting whole breast radiation without regional nodal radiation, based on its equivalence in efficacy and toxicity demonstrated in the moderately hypofractionated trials.\textsuperscript{173} Although these abbreviated courses of RT of 40–42.5 Gy in 15–16 fractions are the NCCN Panel’s preferred fractionation schema for whole breast radiation, the conventionally fractionated regimen of 46–50 Gy in 23–25 fractions may be used in selected patients. The RT boost doses intended to decrease rate of local recurrence are 10–16 Gy in 4–8 fractions.

Ultra-hypofractionated WBRT of 28.5 Gy delivered as 5 (once weekly) fractions may be considered in select patients with pTis/T1/T2/N0 aged >50 years after BCS, though the optimal fractionation for the boost delivery is unknown for this regimen. Alternatively, 26 Gy in 5 daily fractions over one week may be considered, though data beyond 5 years for local relapse or toxicity are not yet available for this regimen and should be discussed with patients prior to its use. The panel also notes that when using ultra-hypofractionated dosing, it is essential to use 3-D planning to minimize inhomogeneity and exposure to heart and lung.

**Chest Wall Radiation**

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. Chest wall scar boost may be delivered with or without bolus using electrons or photons.

**NCCN Recommendations for Chest Wall Radiation**

The NCCN Panel recommends dose of 45–50.4 Gy in 25–28 fractions to the chest wall. A boost at the scar at the dose of 1.8–2 Gy per fraction to a total dose of approximately 60–66 Gy may be considered in some cases based on risk. Special consideration should be given to the use of bolus material to ensure that the skin dose is adequate, particularly in the case of inflammatory breast cancer.

**Regional Nodal Irradiation**

Two studies, MA.20 and EORTC 22922/10925 evaluated the addition of regional nodal irradiation (RNI) to the internal mammary nodes and the upper axillary nodes, including the supraclavicular region, in addition to WBRT or chest wall irradiation after BCS 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.\textsuperscript{181} The distant recurrences were reduced from 17.3\% to 13.4\%.\textsuperscript{181} An improvement in DFS was seen from 77\% to 82\% at 10 years in those who received RNI compared with those who did not.\textsuperscript{181} In EORTC 22922/10925, regional RT 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.\textsuperscript{182} Results of 15.7 years follow-up showed that breast cancer mortality (19.8\% vs 16\%; 95\% CI, 0.70–0.94) and breast cancer recurrence (27.1\% vs 24.5\%; 95\% CI, 0.77%–0.98\%) were reduced with internal mammary and medial supraclavicular RT.\textsuperscript{183}

The independent contribution of internal mammary nodal RT as a component of RNI continues to be debated as it is associated with higher risk of cardiac and lung toxicity, and data regarding its benefits are conflicting (discussed in detail below).

**NCCN Recommendation for RNI**

When considering RNI, anatomic variations across patients result in significant differences in prescription depth and field design. The NCCN Panel therefore recommends contouring the individual nodal basins that are at-risk using one of the various breast atlases, to ensure adequate RT coverage.\textsuperscript{184,185}

The recommended dose for RNI is 45–50.4 Gy in 25–28 fractions to the regional nodal fields. A supplemental boost of RT can be delivered to grossly involved or enlarged lymph nodes (ie, internal mammary or clavicular) that have not been surgically addressed.

**Accelerated Partial Breast Irradiation**

Several large, randomized trials have been published using various forms of APBI rather than WBRT after BCS. Most of these studies have found that rates of local control in selected low-risk patients with early-stage breast cancer are equal to those treated with WBRT.\textsuperscript{42,44,186–188} In the NSABP B-39 trial, 10-year cumulative incidence of IBTR with APBI was 4.6\% compared with 3.9\% with WBRT, yielding an absolute difference of 0.7\% with an HR of 1.22 (90\% CI, 0.94–1.58) that did not meet the pre-specified criteria for equivalence.\textsuperscript{41} However, given the small magnitude in IBTR differences between WBRT and APBI, it is not likely to be of clinical significance in appropriately selected patients.

QOL, toxicity, and cosmetic outcomes have generally been comparable or slightly favored APBI in randomized trials. For example, the IMPORT-LOW study compared WBRT with partial breast irradiation delivered as 40 Gy in 15 once-daily fractions using reduced-size breast tangents and found less breast firmness, less change in breast appearance, and lower average number of adverse events per person with partial breast irradiation.\textsuperscript{186,189}

The University of Florence compared WBRT with intensity modulated APBI (30 Gy in 5 fractions, delivered every other day), and 10 year results have shown that APBI produced less acute and late toxicity, and better cosmetic outcomes.\textsuperscript{187} However, the RAPID trial found significantly higher rates of fair/poor cosmetic outcome with 3-D conformal APBI delivered as 38.5 Gy in 10 twice-daily fractions.\textsuperscript{32,190} The majority of APBI patients on NSABP B-39 were treated with the same external beam regimen, and treatment-related toxicities were not different for APBI versus WBRT as currently reported.\textsuperscript{41} Cosmetic outcome analysis however, is pending.

**NCCN Recommendation for APBI**

The panel accepts the updated ASTRO APBI consensus statement for guidance on APBI.\textsuperscript{191} The NCCN Panel recommends APBI for any BRCA negative patient who meets the ASTRO 2016 “suitable” criteria defined as age 50 years and older, ER-positive invasive ductal carcinoma measuring ≤2 cm (pT1 disease) with negative margin widths of ≥2 mm, and no lymphovascular invasion and also permits APBI in women aged 50 years and older with screen-detected low- or intermediate-grade DCIS measuring ≤2.5 cm, resected with ≥3 mm margins. The panel prefers the APBI regimen and method followed in the trial by University of Florence (30 Gy/5 fractions 1 per day delivered using IMRT).\textsuperscript{187} The panel encourages participation in clinical trials for patients who do not meet the previously discussed criteria.

**Adjuvant RT After BCS**

Those who have a positive lymph node have a high risk of recurrence. Therefore, after BCS, WBRT is strongly recommended with or without boost to tumor bed for node-positive disease (category I 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 EBCTCG showing reduction in 10-year risk of recurrence in those who received WBRT versus those who did not (19\% vs 35\%; RR, 0.52; 95\% CI, 0.48–0.56).\textsuperscript{117} 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.\textsuperscript{117}

For patients with a pathologically confirmed, focally positive margin without extensive intraductal component, who do not undergo re-excision after BCS, the use of a higher radiation boost dose to the tumor bed may be considered, since generally a boost to the tumor bed is recommended for patients at higher risk of recurrence.

**Regional Nodal Irradiation After BCS**

The reduction in the risk of locoregional and distant recurrence and improvement in DFS seen in the MA.20 and EORTC 22922/10925 trials,\textsuperscript{181,182} and the reduction in breast
cancer mortality with 15-year follow-up of the EORTC 22922 patients, support the importance of RNI after BCS.

As mentioned previously, routine inclusion of the internal mammary nodes as a component of RNI remains somewhat controversial due to the associated cardiac and lung toxicities. A Korean trial KROG 08-06 studied the independent effect on DFS of RT to internal mammary nodes after BCS or mastectomy for node positive disease, randomizing patients to RT with internal mammary RT versus RNI without internal mammary RT. Radiation to the internal mammary nodes did not significantly improve the DFS in patients with node-positive breast cancer. However, there was a statistically significant benefit in outcomes with internal mammary nodal RT for patients with medi- or centrally located tumors. Conflicting data have arisen from the Danish Breast Cancer Cooperative Group that recently reported 15-year follow-up of their study on RT to internal mammary nodes in patients (n=3,089) with positive nodes and early-stage breast cancer. In this study, RT to the internal mammary nodes was delivered to right-sided patients (n=1,491) while no RT to internal mammary nodes was delivered to left-sided patients (n=1,598). The study reported a 15-year improved OS rate of 60.1% with RT to internal mammary nodes compared with 55.4% with no RT to internal mammary nodes. Improvements were also seen with respect to risk of developing distant recurrence and breast cancer specific mortality favoring RT to internal mammary nodes.

Clinical judgment is needed when determining inclusion of the internal mammary nodes during RNI. Therefore, the NCCN Panel no longer specifies the fields that should be included for RNI and refers to it as “comprehensive RNI.” According to the panel, patient selection should consider risks versus benefits, including long-term organ (cardiac and lung) toxicities, comorbidities of the patient, age, and life expectancy. In including RT to the internal mammary nodes, meticulous treatment planning with normal tissue dose constraints is mandatory.

RNI After BCS for Node-Negative Disease
The NCCN Panel recommends consideration of comprehensive RNI in patients with central/medial tumors (in accordance with EORTC 22922 trial criteria) and in accordance with the MA.20 criteria-T3 tumors, as well as those with T2 tumors who have undergone limited axillary dissection (<10 lymph nodes) and also have other risk factors, including high-grade histology, ER-negative disease, or extensive lymphovascular invasion.

RNI After BCS for Node-Positive Disease
For those with 1 to 3 positive nodes, if a patient meets all of the following criteria: cT1–T2, cN0; did not receive preoperative chemotherapy; and has 1 or 2 positive SLNs the use of comprehensive RNI with or without the intentional inclusion of the axilla is at the discretion of the radiation oncologist. If patients do not meet all the criteria listed, the NCCN Panel recommends WBRT with inclusion of any portion of the undissected axilla at risk (category 1) with strong consideration of comprehensive RNI.

For those with ≥4 positive nodes, the NCCN Panel recommends comprehensive RNI with inclusion of any portion of the undissected axilla at risk (category 1).

RT After BCS in Older Adults With ER-Positive Tumors
WBRT as a component of BCT does not affect breast cancer specific survival in selected patients 70 years of age or older with more indolent disease. In a study of patients with clinical stage LER-positive breast cancer who were 70 years of age or older at diagnosis, patients were randomized to receive BCS with WBRT or BCS alone, both with tamoxifen for 5 years. Locoregional recurrence rates were 1% in the BCS, radiation, and tamoxifen arm and 4% in the BCS plus tamoxifen arm. There were no differences in OS, DFS, or need for mastectomy. These results were confirmed in an updated analysis of this study with a median follow-up of 12.6 years. At 10 years, a statistically significant reduction in IBTR was seen with RT with 90% of patients in the BCS and tamoxifen arm compared with 98% in the BCS plus radiation and tamoxifen arm. Concordant results have been demonstrated in other studies of similar design. Whether the increase in local relapse without RT is relevant for an individual patient should be individualized after a discussion of the risks and benefits of RT and patient commitment to 5 years of endocrine therapy if RT omission is being considered.

The NCCN Guidelines allow for the use of BCS (pathologically negative margin required) with 5 years of tamoxifen or an aromatase inhibitor, without breast irradiation, for patients 70 years of age or older with clinically negative lymph nodes and ER-positive, T1 breast cancers (category 1).

Adjuvant RT After Mastectomy
Postmastectomy RT for 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 patients with positive ALNs after mastectomy and ALN dissection. In these trials, the ipsilateral chest wall and the ipsilateral locoregional lymph nodes were irradiated. The results of EBCTCG meta-analyses show that RT after mastectomy and axillary node dissection reduced both recurrence and breast cancer mortality in the patients with 1 to 3 positive lymph nodes even when systemic therapy was administered. According to the NCCN Panel, post-mastectomy radiation to chest wall is recommended in
In patients with negative nodes, tumor ≤5 cm, and clear margins (≥1 mm), postmastectomy RT is typically not recommended. However, the panel has noted that it may be considered in subsets of these patients with high-risk features. Based on the inclusion criteria of patients who were node negative enrolled in the RNI trials (MA-20 and EORTC 22922), any patients with high-risk features including central/medial tumors, T3 tumors, or tumors ≥2 cm with <10 axillary nodes removed and at least one of the following: grade 3, ER-negative, or lymphovascular invasion, should be considered for PMRT with RNI to include any undissected axilla at risk. Features in node-negative tumors that predict a high rate of local recurrence include primary tumors >5 cm or positive pathologic margins.

In patients with positive pathologic margin, if re-resection to negative margins is not possible, the panel recommends strongly considering chest wall irradiation with the addition of comprehensive RNI including any portion of the axilla at risk. Chest wall irradiation should be considered with addition of comprehensive RNI including any portion of the axilla at risk in those with tumors >5 cm. In patients with tumors ≤5 cm and negative margins but ≤1 mm, chest wall irradiation should be considered with consideration of comprehensive RNI including any portion of the undissected axilla at risk only in those with high-risk features.

**Considerations for RT in Patients Receiving Preoperative Systemic Therapy**

The panel recommends that decisions related to administration of adjuvant RT for patients receiving preoperative systemic chemotherapy should be made based on maximal stage (ie, clinical/anatomic stage, tumor characteristics) at diagnosis (before preoperative systemic therapy) and pathologic stage at definitive surgery (after preoperative systemic therapy). Data from numerous studies in patients with stage III disease suggest that postoperative RT improves local control even for patients who have a pathologic complete response to neoadjuvant chemotherapy.

**RT After Preoperative Therapy and BCS**

Those who have clinically node-negative disease at diagnosis that remains pathologically node negative at definitive surgery (after systemic therapy) should receive adjuvant RT to the whole breast with the addition of boost to the tumor bed after SLNB.

Patients who have clinically/radiographically positive nodes at diagnosis and convert to clinically/radiographically negative nodes after preoperative chemotherapy are candidates for the NSABP B-51 trial assessing the benefit of RNI. Until the results of this trial become available, the existing data suggest patients with node-positive disease at presentation are at high risk for locoregional recurrence and should be considered to receive comprehensive RNI with inclusion of any portion of the undissected axilla at risk.

Patients who have clinically/radiographically positive nodes at diagnosis who convert to clinically/radiographically negative nodes after preoperative chemotherapy but are found to have persistent nodal disease on SLNB are candidates for the ALLIANCE 11202 trial assessing whether ALND can be safely replaced with axillary RT. ALND is the standard arm of this trial; however, in the event that a neoadjuvant therapy patient with node-positive disease (ypN1+) does not undergo a complete axillary dissection, all levels of the undissected axilla should be included with the RT.

**RT After Preoperative Therapy and Mastectomy**

Those who have clinically positive nodes at diagnosis that respond to preoperative systemic therapy and become node-negative should be strongly considered for receiving RT to the chest wall and comprehensive RNI with inclusion of any portion of the undissected axilla at risk based on the previous discussion.

For those with positive nodes (ypN1+) after preoperative systemic therapy, axillary dissection is the standard treatment arm of the ongoing Alliance 11202 trial. However, if RT is indicated, it should include chest wall along with comprehensive RNI with inclusion of any portion of the undissected axilla at risk.

Those who have node-negative disease at diagnosis and after preoperative systemic therapy and whose axilla was assessed using SLNB or axillary node dissection may forego RT.

Two prospective trials are ongoing and will prospectively evaluate the benefit of RT in patients treated with neoadjuvant therapy (NSABP B-51/RTOG 1304 [Clinical-Trial.gov identifier: NCT01872975] and the Alliance A011202/MAC19 trial [NCT01901094]).

**Sequencing of RT and Systemic Therapy**

If chemotherapy and radiation are indicated after surgery, adjuvant radiation is typically delivered after the completion of chemotherapy.

This recommendation is based on results of the “Upfront-Outback” trial in which
patients who had undergone BCS and axillary dissection were randomly assigned to receive chemotherapy after RT or RT after chemotherapy. The initial results showed an increased rate of local recurrence in the group with delayed RT at a median follow-up of 58 months; however, differences in rates of distant or local recurrence were not statistically significant when the 2 arms were compared at 135-month follow-up. Although it is common for RT to follow chemotherapy when chemotherapy is indicated, based on data from prospective and retrospective studies, CMF (cyclophosphamide/methotrexate/fluorouracil) and RT may be given concurrently.

Data from multiple studies of patients treated with endocrine therapy before, during or after RT suggest no difference in outcomes or toxicity. Therefore, according to the NCCN Panel, sequential or concurrent endocrine therapy with RT is acceptable. However, due to compounding side effects, initiating endocrine therapy at the completion of RT may be preferred.

When adjuvant capecitabine is indicated, because it is a known radiosensitizing agent with potential to increase toxicity to normal tissue, it should be given after completion of adjuvant RT. When adjuvant olaparib is used, the panel recommends that olaparib be given after completion of RT. In the OlympiA trial, olaparib was not administered concurrently with RT and limited data are available on safety of concurrent administration.

Adjuvant HER2-targeted therapy may be delivered concurrently with RT. Data from clinical trials in the adjuvant setting do not suggest an increased complication rate with the concurrent administration of HER2-targeted therapies with adjuvant RT.

References


## Individual Disclosures for the NCCN Breast Cancer Panel

<table>
<thead>
<tr>
<th>Panel Member</th>
<th>Clinical Research Support/Data Safety Monitoring Board</th>
<th>Scientific Advisory Boards, Consultant, or Expert Witness</th>
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<td>Marilyn Leith, MD</td>
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<td>Puma Biotechnology</td>
<td>None</td>
<td>Cancer CareCore National, LLC dba eviCore Healthcare; Daiichi-Sankyo Co., Eli Lilly and Company; Genentech, Inc.; Novartis; Puma Biotechnology; Roche Laboratories, Inc.</td>
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<td>Janice Lyons, MD</td>
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<td>Laura H. Rosenberger, MD, MS</td>
<td>Luminex, Inc.</td>
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<td>Hope S. Ruggi, MD</td>
<td>AstraZeneca Pharmaceuticals LP; Apogen, Biotheranostics, Geisinger Health System, Gilead Sciences, Inc.; LillyMacrogenics, Merck &amp; Co., Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; PolyPath; Roche Laboratories, Inc.; Seattle Genetics, Inc.; Semma</td>
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<td>Amy Stquito, MD</td>
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<td>Hetsen Soliman, MD</td>
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<td>Erica M. Stringer-Resor, MD</td>
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<td>Melinda L. Tall, MD</td>
<td>ABA, Inc.; Bayer Healthcare, Biotronik, EMD Serono, G1 Therapeutics; Genentech, Inc.; Immunomedics, Inc.; Merck &amp; Co., Inc.; Oncologic Medical, Pfizer Inc.; Puma Biotechnology; TESSAR, Inc.; Varena Pharmaceuticals Incorporated</td>
<td>AstraZeneca Pharmaceuticals LP; Blueprint Medicine; Genentech, Inc.; Guardant; Merck &amp; Co., Inc.; Natera; Novartis Pharmaceuticals Corporation, Oncologic Medical, sanofi-aventis U.S.</td>
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<td>Karl W. Woinski, MD</td>
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<td>Jessica S. Young, MD</td>
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The NCCN Guidelines Staff has no conflicts to disclose.

*The following individuals have disclosed that they have an employment/governing board, patient, equity, or royalty:

- Marilyn Leith, MD, Alliance for Clinical Trials in Oncology
- Karen Lise Smith, MD, MPH, Abbott Laboratory/AbbVie, Inc.