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Release date: February 10, 2019; Expiration date: February 10, 2020

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Breast Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Breast Cancer

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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Breast Cancer, Version 3.2018

Featured Updates to the NCCN Guidelines

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ABSTRACT

These NCCN Guidelines Insights highlight the updated recommendations for use of multigene assays to guide decisions on adjuvant systemic chemotherapy therapy for women with hormone receptor–positive, HER2-negative early-stage invasive breast cancer. This report summarizes these updates and discusses the rationale behind them.

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SYSTEMIC ADJUVANT TREATMENT: **NODE-NEGATIVE** - HORMONE RECEPTOR-POSITIVE - HER2-NEGATIVE DISEASE^c

^cSee Principles of HER2 Testing (BINV-A).

^yMixed lobular and ductal carcinoma should be graded based on the ductal component and treated based on this grading. For metaplastic carcinoma, the prognostic value of the histologic grading is uncertain. However, when a specific histologic subtype of metaplastic carcinoma is present and accounts for more than 10% of the tumor, the subtype is an independent prognostic variable.

^zConsider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy.

^{aa}Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-J).

^{bb}Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. See Adjuvant Endocrine Therapy (BINV-J) and Preoperative/Adjuvant Therapy Regimens (BINV-K).

^{cc}There are limited data to make chemotherapy recommendations for those >70 y of age. See NCCN Clinical Practice Guidelines for Older Adult Oncology.

^{gg}Other prognostic multigene assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy. See Multigene Assays for Consideration of Addition of Adjuvant Systemic Chemotherapy to Adjuvant Endocrine Therapy (BINV-M).

^{hh}Patients with T1b tumors with low grade histology should be treated with endocrine monotherapy as the TAILORx trial did not include patients with such tumors.

ⁱⁱConsider the use of adjuvant chemotherapy in women 50 years of age or younger with a recurrence score of 16–25 based on an exploratory analysis from the TAILORx study demonstrating lower distant recurrences in women 50 years of age or younger randomized to chemotherapy.

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Overview

Breast cancer is the most common malignancy in women in the United States and is second only to lung cancer as a cause of cancer death. The American Cancer Society has estimated that 271,270 Americans will be diagnosed with breast cancer and 42,260 will die of disease in the United States in 2019.¹ The therapeutic options for patients with noninvasive or invasive breast cancer are complex and varied. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer include up-to-date guidelines for the clinical management of patients with carcinoma in situ, invasive breast cancer, Paget's disease, Phyllodes tumor, inflammatory breast cancer, and breast cancer during pregnancy. These guidelines are developed by a multidisciplinary panel of representatives from NCCN Member Institutions with breast cancer-focused expertise in the fields of medical oncology, surgical oncology, radiation oncology, pathology, reconstructive surgery, and patient advocacy.

In a recent version of these guidelines, the NCCN Breast Cancer Panel included updated recommendations for the use of multigene assays to guide decisions on adjuvant systemic chemotherapy therapy for women with

hormone receptor (HR)–positive, HER2-negative early-stage invasive breast cancer. This report summarizes these updates and discusses the rationale behind them.

Adjuvant Systemic Therapy for HR-Positive/HER2-Negative Tumors

In patients with early-stage breast cancer, systemic adjuvant therapy is administered to reduce risk of cancer recurrence. Women with HR-positive, HER2-negative tumors receive adjuvant endocrine therapy to reduce the risk of recurrence, and those deemed at high risk for distant recurrence despite adjuvant endocrine therapy receive adjuvant chemotherapy. The incremental benefit of adding adjuvant chemotherapy to endocrine therapy in patients with a low clinical risk of recurrence, such as those with very small, low-grade, lymph node–negative tumors, is relatively small.² The decision whether to administer adjuvant chemotherapy in patients with HR-positive, HER2-negative tumors is based on many factors, including lymph node status, tumor size and grade, lymphovascular invasion, age, comorbid conditions, and/or results of a gene expression profile test using multigene assays.

SYSTEMIC ADJUVANT TREATMENT: **NODE POSITIVE** - HORMONE RECEPTOR-POSITIVE - HER2-NEGATIVE DISEASE^c

^cSee Principles of HER2 Testing (BINV-A).

^yMixed lobular and ductal carcinoma should be graded based on the ductal component and treated based on this grading. For metaplastic carcinoma, the prognostic value of the histologic grading is uncertain. However, when a specific histologic subtype of metaplastic carcinoma is present and accounts for more than 10% of the tumor, the subtype is an independent prognostic variable.

^zConsider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy.

^{aa}Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-J).

^{bb}Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. See Adjuvant Endocrine Therapy (BINV-J) and Preoperative/Adjuvant Therapy Regimens (BINV-K).

^{cc}There are limited data to make chemotherapy recommendations for those >70 y of age. See NCCN Clinical Practice Guidelines for Older Adult Oncology.

^{jj}In N1mi and N1, multigene assays are prognostic and not proven to be predictive of chemotherapy benefit but can be used to identify a low risk population that when treated with proper endocrine therapy may derive little absolute benefit from chemotherapy. Regarding the 21 gene RT-PCR assay, a secondary analysis of a prospective trial suggests that the test is predictive for women with 1-3 involved ipsilateral axillary lymph nodes. Other multigene assays have not proven to be predictive of chemotherapy benefit.

^{kk}See Multigene Assays for Consideration of Addition of Adjuvant Systemic Chemotherapy to Adjuvant Endocrine Therapy (BINV-M).

^{ll}There are few data regarding the role of multigene assays in women with four or more ipsilateral axillary lymph nodes. Decisions to administer adjuvant chemotherapy for this group should be based on clinical factors.

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Multigene Assays

Several commercially available gene-based assays are useful in determining prognosis through predicting distant recurrence, local recurrence, or survival. Of these, only one, the 21-gene assay (Oncotype Dx, Genomic Health, Inc.) has been clinically validated for predicting the benefit of adding adjuvant chemotherapy to further reduce the risk of recurrence.

21-Gene Assay

Node-Negative, HR-Positive, HER2-Negative Breast Cancer

The 21-gene recurrence score (RS) is one of the most validated multigene assays. The RS is helpful in determining the prognosis in women with HR-positive, HER2-negative tumors treated with endocrine therapy alone by predicting locoregional and distant recurrence.³⁻⁵ This assay has also been validated to predict the benefit from adding adjuvant chemotherapy to adjuvant endocrine therapy for women with HR-positive, HER2-negative, node-negative breast cancer.⁶⁻⁸

Among patients with T1b/T1c and T2, lymph node-negative, HR-positive, HER2-negative tumors with RS

between 0 and 10, the risk of distant recurrence is low, and these patients derive no incremental benefit from the addition of adjuvant chemotherapy to endocrine therapy.^{7,9} At the other end of the spectrum, patients with node-negative, HR-positive, HER2-negative cancers with high RS (≥ 31) have a higher risk of distant recurrence, and secondary analyses of prospective studies show that these patients derive a clear benefit from adjuvant chemotherapy.^{7,9}

For patients with an intermediate RS (11–25), the recently reported TAILORx trial of postmenopausal women (N=6,711) with node-negative, HR-positive, HER2-negative breast cancer showed similar disease-free survival rates at 9 years in those who received adjuvant chemotherapy followed by endocrine therapy compared with endocrine therapy alone.⁹ However, a subset analysis of women aged ≤ 50 years with RS of 16 to 25 showed significantly lower rates of distance recurrence with the addition of adjuvant chemotherapy to endocrine therapy.⁹ The cutoff for low, intermediate, and high RS was different in TAILORx versus NSABP B-20. The NSABP-B20 was the first trial to validate the 21-gene assay as both a prognostic and a predictive tool, and identified RS cutoffs to predict the magnitude of chemotherapy benefit in patients with node-negative, HR-positive breast cancer.⁷

MULTIGENE ASSAYS FOR CONSIDERATION OF ADDITION OF ADJUVANT SYSTEMIC CHEMOTHERAPY TO ADJUVANT ENDOCRINE THERAPY^a

Assay	Predictive	Prognostic	NCCN Category of Preference	NCCN Category of Evidence and Consensus	Recurrence Risk	Treatment Implications (references on next page)
21-gene (Oncotype Dx) (for pN0 or node negative)	Yes	Yes	Preferred	1	<26	Patients with T1b/c and T2, hormone receptor-positive, HER2-negative and lymph node-negative tumors, with risk scores (RS) between 0-10 have a risk of distant recurrence of less than 4% and those with RS 11-25, derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective TAILORx study. ¹ In women 50 years of age or younger, with RS 16-25 addition of chemotherapy to endocrine therapy was associated with a lower rate of distant recurrence compared with endocrine monotherapy. Consideration should be given for the addition of chemotherapy to endocrine therapy in this group. ¹
					26-30	In patients with T1 and T2, hormone receptor-positive, HER2-negative and lymph node-negative tumors and a RS of 26-30, the omission of chemotherapy has not been studied prospectively. Clinicians should consider additional clinical and pathological factors with regard to the addition of chemotherapy to endocrine therapy in decision-making. ²
					≥31	For patients with T1b/c and T2, hormone receptor-positive, HER2-negative and lymph node-negative tumor RS ≥31, the addition of chemotherapy to endocrine therapy is recommended. ²
21-gene (Oncotype Dx) (for pN+ or node positive)	N/A* *awaiting results of Rxponder study	Yes	Other	2A	Low (<18)	The RS is prognostic in women with hormone receptor-positive, lymph node positive tumors receiving endocrine monotherapy. ³⁻¹⁰ A secondary analysis of a prospective registry of women with hormone receptor-positive, HER2-negative, lymph node positive tumors demonstrated a 5 year risk of distant recurrence of 2.7% in patients with a RS of <18 treated with endocrine monotherapy. ⁹ In the West German Plan B study, 110 women with hormone receptor-positive, HER2-negative, lymph node-positive tumors and a RS of <11, showed a 5 year disease free survival of 94.4% when treated with endocrine monotherapy. ⁶ For hormone receptor-positive, HER2-negative, lymph node-positive tumors, clinicians should be aware that the optimal RS cut-off (< 11 vs < 18) is still unknown both for prognosis (risk of recurrence) as well as prediction of chemotherapy benefit.
					Intermediate (18-30) or High (≥31)	In a secondary analysis of the SWOG 8814 trial of women with hormone receptor-positive, lymph node-positive tumors, high RS (≥31) was predictive of chemotherapy benefit. Because of a higher risk of distant recurrence, patients with hormone receptor-positive, 1-3 positive lymph nodes and RS of ≥18 should be considered for adjuvant chemotherapy in addition to endocrine therapy. ³
70-gene (MammaPrint) (for node negative and 1-3 positive nodes)	Not determined	Yes	Other	1	Low	With a median follow-up of 5 years, among patients at high clinical risk and low genomic risk, the rate of survival without distant metastasis in this group was 94.7% (95% confidence interval, 92.5% to 96.2%) among those who did not receive adjuvant chemotherapy. Among patients with 1-3 positive nodes, the rates of survival without distant metastases were 96.3% (95% CI, 93.1 to 98.1) in those who received adjuvant chemotherapy versus 95.6% (95% CI, 92.7 to 97.4) in those who did not receive adjuvant chemotherapy. ¹¹ Therefore, the additional benefit of adjuvant chemotherapy may be small in this group.
					High	
50-gene (PAM 50) (for node negative and 1-3 positive nodes)	Not determined	Yes	Other	2A	Node negative: Low (0-40)	For patients with T1 and T2 hormone receptor-positive, HER2-negative, lymph node-negative tumors, a risk of recurrence score in the low range, regardless of T size, places the tumor into the same prognostic category as T1a-T1b, N0, M0. ¹²
					Node negative: Intermediate (41-60)	
					Node negative: High (61-100)	In patients with hormone receptor-positive, HER2-negative, 1-3 positive lymph nodes with low risk of recurrence score, treated with endocrine therapy alone, the distant recurrence risk was less than 3.5% at 10 years ¹² and no distant recurrence was seen at 10 years in TransATAC study in a similar group. ¹³
					Node positive: Low (0-40)	
12-gene (EndoPredict) (node negative and 1-3 nodes)	Not determined	Yes	Other	2A	Low (<3.3287)	For patients with T1 and T2 hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a 12-gene low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a-T1b, N0, M0. ¹³ In ABCSG 6/8, patients in the low risk group has risk of distant recurrence of 4% at 10 years and in the TransATAC study, patients with 1-3 positive nodes in the low-risk group had a 5.6% risk of distant recurrence at 10 years. ¹³
					High (>3.3287)	
Breast Cancer Index (BCI)	Not determined	Yes	Other	2A	Low risk of late occurrence (0-5)	For patients with T1 and T2 hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a BCI in the low-risk range, regardless of T size, places the tumor into the same prognostic category as T1a-T1b, N0, M0. There are limited data as to the role of BCI in hormone receptor-positive, HER2-negative, and lymph node-positive breast cancer. ¹³
					High risk of late occurrence (5.1-10)	

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BINV-M
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Node-Positive, HR-Positive, HER2-Negative Breast Cancer

In the West German Study Group PlanB trial, women (N=110) with node-positive, HR-positive, HER2-negative tumors and RS <11 were found to have a 5-year disease-free survival of 94.4% when treated with endocrine therapy alone.¹⁰ In a secondary analysis of a prospective registry of women with node-positive, and HR-positive, HER2-negative tumors, the 5-year risk of distant recurrence in patients with RS <18 who were treated with endocrine therapy alone was 2.7%.¹¹ These results suggest that in patients with limited nodal disease (1-3 positive lymph nodes) and a low RS, the absolute benefit from chemotherapy is likely to be very small.^{10,11}

There is a clear benefit from adjuvant chemotherapy in patients with node-positive, HR-positive, HER2-negative tumors if they have a high RS (≥31). In a secondary analysis of the SWOG-8814 trial of women with node-positive, HR-positive tumors, high RS (≥31) was predictive of chemotherapy benefit. This study evaluated breast cancer specimens from node-positive, HR-positive postmenopausal women (N=367) randomized

to endocrine therapy with tamoxifen alone or chemotherapy with CAF (cyclophosphamide/doxorubicin/fluorouracil) followed by tamoxifen.⁶ Compared with tamoxifen alone, treatment with CAF among women with high RS (≥31) resulted in improved 10-year disease-free survival (55% vs 43%; hazard ratio [HR], 0.59; 95% CI, 0.35-1.01) and overall survival (73% vs 54%; HR, 0.56; 95% CI, 0.31-1.02).⁶

The absolute benefit of chemotherapy in patients with limited lymph node involvement and RS ≤25 remains to be determined. The ongoing SWOG-S1007 RxPONDER trial (ClinicalTrials.gov identifier: NCT01272037) assigned women with 1 to 3 positive lymph nodes and HR-positive, HER2-negative breast cancer and RS ≤25 to standard endocrine therapy either with or without adjuvant chemotherapy. The results of this trial are expected to determine the benefit (if any) for chemotherapy in this group of patients.

70-Gene Assay

Results from the randomized MINDACT trial¹² demonstrated that the 70-gene assay (MammaPrint, Agendia)

MULTIGENE ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC CHEMOTHERAPY^a

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^aMultigene assays provide prognostic and therapy-predictive information that complements T,N,M and biomarker information. Use of these assays is not required for staging. The 21-gene assay (Oncotype Dx) is preferred by the NCCN Breast Cancer Panel for node negative breast cancer. Other prognostic multigene assays can provide additional prognostic information in patients with 1-3 positive lymph nodes but are unknown if predictive of chemotherapy benefit in 1-3 positive lymph nodes

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BNV-M
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can identify a subset of patients who have a low likelihood of distant recurrence despite high-risk clinical features (based on tumor size, tumor grade, nodal status). In this trial, 79% of patients had node-negative disease and 21% had 1 to 3 positive lymph nodes, and all patients underwent risk assessment using clinical criteria (using Adjuvant!Online) and genomic risk assessment using the 70-gene assay.

Patients with low-risk disease according to both clinical criteria and genomic assay results did not receive adjuvant chemotherapy, whereas those categorized as high risk by both assessments received chemotherapy. Patients with discordant results (ie, either high clinical risk/low genomic risk or low clinical risk/high genomic risk) were randomized to the chemotherapy group or the no-chemotherapy group based on either the clinical or the genomic result. The primary outcome of the study was met with the demonstration that among those with high clinical risk/low genomic risk, the 5-year rate of survival with no distant metastasis in those did not receive adjuvant chemotherapy was 94.7% (95% CI, 92.5–96.2).¹²

In the intention-to-treat population, among patients at high clinical risk/low genomic risk using the 70-gene assay, the 5-year rate of survival with no distant metastasis

in those who received chemotherapy was 95.9% (95% CI, 94.0–97.2) versus 94.4% (95% CI, 92.3–95.9) in those who did not receive chemotherapy (adjusted HR for distant metastasis or death with chemotherapy vs no chemotherapy, 0.78; 95% CI, 0.50–1.21).¹² Among patients at low clinical risk/high genomic risk, the 5-year rate of survival with no distant metastasis was 95.8% with chemotherapy (95% CI, 92.9–97.6) versus 95.0% (95% CI, 91.8–97.0%) without chemotherapy (adjusted HR for distant metastasis or death with chemotherapy vs no chemotherapy, 1.17; 95% CI, 0.59–2.28). These data suggest that the results of the 70-gene signature do not provide evidence for making recommendations regarding chemotherapy for patients at low clinical risk.¹²

In a subgroup analysis by nodal status, among node-negative patients with high clinical risk/low genomic risk, the 5-year rate of survival with no distant metastasis was 95.7% (95% CI, 93.0–97.4) in those who received adjuvant chemotherapy compared with 93.2% (95% CI, 90.1–95.4) in those who did not receive chemotherapy.¹² Among patients with 1 to 3 positive lymph nodes, the rates of survival without distant metastases were 96.3% (95% CI, 93.1–98.1) in those who received adjuvant chemotherapy versus 95.6% (95% CI, 92.7–97.4) in those who did not

receive adjuvant chemotherapy.¹² These data suggest that the additional benefit of adjuvant chemotherapy in patients with high-clinical risk/low genomic risk is likely to be small.

50-Gene Assay

The 50-gene assay (PAM50; NanoString) risk of recurrence (ROR) score stratifies patients with HR-positive disease into high-, medium-, and low-risk groups. Several studies have demonstrated the prognostic value of ROR score in estimating risk of disease recurrence.^{13–15}

In a study using the Danish Breast Cancer Cooperative Group database, patients with node-negative tumors and low ROR had a distant recurrence risk of 5.0% (95% CI, 2.9%–8.0%) compared with 17.8% (95% CI, 14.0%–22.0%) in those with high ROR.¹⁴ Based on these analyses, patients with T1 and T2 node-negative HR-positive, HER2-negative tumors and an ROR score in the low range, regardless of tumor size, places the individual in the same prognostic category as those with T1a/T1bN0M0 tumors.¹⁴

In patients with 1 to 3 positive lymph nodes and HR-positive, HER2-negative disease with a low RS, the distant recurrence risk was <3.5% at 10 years with endocrine therapy alone.¹⁴ In the TransATAC study, no distant recurrence was seen at 10 years in a similar group.¹⁵

12-Gene Assay

The EndoPredict assay (Myriad Genetics) uses 12 genes to calculate a prognostic score. This assay appears to be useful in identifying a subgroup of patients with estrogen receptor-positive, HER2-negative tumors at very low risk of recurrence without adjuvant chemotherapy and helpful in identifying patients at low risk for a late recurrence.¹⁶ Based on results of 2 Austrian Breast and Colorectal Cancer Study Group trials, ABCSG-6 and ABCSG-8, patients with node-negative, HR-positive, HER2-negative disease with a low risk score by the 12-gene assay had a 4% risk of distant recurrence at 10 years.¹⁶ The prognostic value of the risk score from the 12-gene assay was found to be independent of conventional clinicopathologic factors. In patients with T1 and T2 node-negative, HR-positive, HER2-negative tumors, a 12-gene low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a–T1bN0M0.

In the TransATAC study, patients with 1 to 3 positive nodes in the low-risk group had a 5.6% risk of distant recurrence at 10 years,¹⁵ suggesting that chemotherapy would be of limited benefit in these women.

Breast Cancer Index

The Breast Cancer Index (BCI) is a combination of 2 profiles, the HOXB13-to-IL17BR expression ratio (H:I ratio)

and the Molecular Grade Index (MGI). Compared with clinical prognostic factors (eg, age, tumor size, tumor grade, lymph node status), the H:I ratio has been shown to be prognostic in the setting of adjuvant tamoxifen monotherapy.^{17–20} The addition of MGI to H:I was determined to provide additional prognostic discrimination, leading to the BCI assay.²¹ In a secondary analysis of the TransATAC trial, BCI was prognostic in node-negative breast cancer for both early (years 0–5) and late (years 5–10) distant recurrence.²² For patients with T1 and T2 node-negative, HR-positive, HER2-negative tumors, a BCI in the low-risk range, regardless of T size, places the tumor into the same prognostic category as T1a/T1bN0M0.

There are limited data regarding the role of BCI in node-positive, HR-positive, HER2-negative breast cancer.

NCCN Recommendations

Use of Multigene Assays

The panel extensively reviewed the available multigene assays, their ability to predict benefit of adjuvant systemic chemotherapy, and their ability to determine prognosis by predicting risk of distant recurrence, and has summarized the treatment implications based on risk scores and nodal status (see table BINV-M, page 122). The panel notes that the multigene assays provide prognostic and therapy-predictive information that complements TNM and biomarker information.

Axillary Lymph Node–Negative, HR-Positive, HER2-Negative Tumors

Small tumors (up to 0.5 cm in greatest diameter) that do not involve the lymph nodes have a favorable prognosis, and therefore adjuvant chemotherapy is not recommended. According to the NCCN Breast Cancer Panel, adjuvant endocrine therapy may be considered in this group of patients to reduce the risk of a second contralateral breast cancer, and due to the small benefit in reducing the risk of local/regional and distant recurrence (category 2B) (see BINV-6, page 120).

For patients with invasive ductal or lobular tumors >0.5 cm in diameter and no lymph node involvement (node-negative), the NCCN panel recommends strongly considering the 21-gene RT-PCR assay to help estimate likelihood of recurrence and benefit from chemotherapy (category 1). The panel has noted that, based on an exploratory analysis from the TAILORx study,⁹ adjuvant chemotherapy may be considered in women aged ≤50 years with a 21-gene RS of 16 to 25. Also, patients with T1b tumors with low-grade histology should be considered for endocrine monotherapy, because the TAILORx study⁹ did not include patients with such tumors (see BINV-6, page 120).

The panel noted that other prognostic multigene assays (listed on BINV-M, pages 122 and 123) may be considered to help estimate recurrence risk, but these assays have not been validated to predict the benefit of systemic chemotherapy. Also, among the other assays, the panel listed the 70-gene assay as a category 1 option based on the results of the prospective MINDACT¹² trial demonstrating its ability to identify patients with a low genomic risk despite a high clinical risk (see BINV-6, page 120), in whom chemotherapy may be omitted without a detrimental effect. High clinical risk in the MINDACT trial was defined as >3 cm N0 or T2N1 for grade 1 tumors, T2N0–1 for grade 2 tumors, and T1c–2N0–1 for grade 3 tumors.

Furthermore, given no difference in outcomes with or without chemotherapy in the discordant low clinical risk/high genomic risk group, the MINDACT study suggests that the 70-gene panel is not useful for guiding systemic chemotherapy decisions in this subgroup of patients.

Because results of different assays may not be concordant with each other and these assays have not been compared head-to-head prospectively, clinicians should only order one of the available assays for a specific patient and tumor.

Axillary Lymph Node–Positive, HR-Positive, HER2-Negative Tumors

For patients with ≥ 4 involved nodes, the panel recommends systemic adjuvant chemotherapy followed by endocrine therapy (category 1) (see BINV-7, page 121).

Patients with <4 involved nodes or with pN1mi and ≤ 2 mm axillary node metastasis are most often candidates for chemotherapy in addition to endocrine therapy. The panel recommends that clinical decision-making for adjuvant chemotherapy be based on elements of clinical risk stratification, such as clinical characteristics, tumor stage, pathology, and comorbid conditions. If the patient is not a candidate for chemotherapy, the panel recommends adjuvant endocrine therapy alone (category 2A) (see BINV-7, page 121).

For patients who are candidates for systemic adjuvant chemotherapy based on clinical characteristics, tumor stage, and pathology, the panel recommends consideration of multigene assays to assess prognosis as a tool to assist with treatment decision-making. The panel notes that in N1mi and N1 tumors, although multigene assays have yet to be proven as predictive

for adjuvant chemotherapy benefit, they are prognostic and can be used to identify low-risk patients who are likely to derive little or no absolute benefit from addition of adjuvant chemotherapy to adjuvant endocrine therapy. Although a secondary analysis of the prospective SWOG-8814 trial showed no benefit for chemotherapy for women with 1 to 3 involved ipsilateral axillary lymph nodes and low RS, it did show benefit for the addition of adjuvant chemotherapy in those with high RS (≥ 31) based on results of the 21-gene assay.⁶ At this time, the optimal RS cutoff (<11 vs <18) to withhold chemotherapy in patients with 1 to 3 positive lymph nodes and HR-positive, HER2-negative breast cancer is still unknown. Results of the RxPONDER trial (ClinicalTrials.gov identifier: NCT01272037) are expected to determine the benefit (if any) of chemotherapy in patients with 1 to 3 positive lymph nodes; HR-positive, HER2-negative disease; and an intermediate risk score. In the MINDACT trial, among patients with 1 to 3 positive nodes who had a high clinical risk of recurrence but low risk based on results of the 70-gene assay, rates of survival were similar between those who received adjuvant chemotherapy in addition to adjuvant endocrine therapy and those received adjuvant endocrine therapy alone, suggesting that chemotherapy could be omitted in this group.¹² Other multigene assays listed on page BINV-M have not proven to be predictive of benefit from chemotherapy (pages 122 and 123).

Among patients who are candidates for systemic adjuvant chemotherapy based on clinical characteristics, tumor stage, and pathology, if multigene assay is not available, the panel recommends systemic adjuvant chemotherapy followed by endocrine therapy (category 1) (see BINV-7, page 121).

Summary

The updated recommendations in the NCCN Guidelines for Breast Cancer provide guidance on the use of multigene assays to either recommend or withhold adjuvant systemic chemotherapy therapy in women with HR-positive, HER2-negative early-stage invasive breast cancer based on nodal status and other clinico-pathologic characteristics.

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