NCCN: Continuing Education

Target Audience: This activity is designed to meet the educational needs of oncologists, nurses, pharmacists, and other healthcare professionals who manage patients with cancer.

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Release date: May 10, 2021; Expiration date: May 10, 2022

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:

Kerrin M. Rosenthal, MA; Kimberly Callan, MS; Genevieve Emberger Hartzman, MA; Erin Hesler; Kristina M. Gregory, RN, MSN, OCN; Rashmi Kumar, PhD; Karen Kanefield; and Kathy Smith.

Individuals Who Provided Content Development and/or Authorship Assistance:

William J. Gradishar, MD, Panel Chair, has disclosed serving as a scientific advisor for AstraZeneca Pharmaceuticals LP, MacroGenics, Inc., Roche Laboratories, Inc./Genentech, Inc., Pfizer Inc., and Seattle Genetics, Inc.

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Sharon H. Giordano, MD, MPH, Panel Member, has disclosed no relevant financial relationships.

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Karen Lisa Smith, MD, MPH, Panel Member, has disclosed receiving equity interest/stock options in Abbott Laboratories and AbbVie, Inc.; and grant/research support from Pfizer Inc.

Hatem Soliman, MD, Panel Member, has disclosed receiving consulting fees from Immunomedics, Eisai, Novartis Pharmaceuticals Corporation, AstraZeneca, and Seattle Genetics.

John H. Ward, MD, Panel Member, has disclosed no relevant financial relationships.

Kari B. Wisinski, MD, Panel Member, has disclosed receiving grant/research support from Pfizer, AstraZeneca, Novartis Pharmaceuticals Corporation, Context, Genentech, and Sanofi; and serving as a scientific advisor for Pfizer, AstraZeneca, and Eisai.

Jennifer L. Burns, Manager, Guidelines Support, NCCN, has disclosed no relevant financial relationships.

To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/disclosures/guidelinepanellisting.aspx.

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Breast Cancer, Version 4.2021
Featured Updates to the NCCN Guidelines

William J. Gradishar, MD[1,*]; Meena S. Moran, MD[2]; Jame Abraham, MD[3,*]; Rebecca Aft, MD, PhD[4]; Doreen Agnese, MD[5]; Kimberly H. Allison, MD[6,*]; Sarah L. Blair, MD[7]; Harold J. Burstein, MD, PhD[8]; Chau Dang, MD[9,*]; Anthony D. Elias, MD[10,*]; Sharon H. Giordano, MD, MPH[11,*]; Matthew P. Goetz, MD[12,*]; Lori J. Goldstein, MD[13]; Sara A. Hurvitz, MD[14,*]; Steven J. Isakoff, MD, PhD[15]; Rachel C. Jankowitz, MD[16]; Sara H. Javid, MD[17]; Jairam Krishnamurthy, MD[18]; Marilyn Leitch, MD[19]; Janice Lyons, MD[3]; Jennifer Matro, MD[16]; Ingrid A. Mayer, MD[20,*]; Joanne Mortimer, MD[21]; Ruth M. O'Regan, MD[22]; Sameer A. Patel, MD[13]; Lori J. Pierce, MD[23]; Hope S. Rugo, MD[24]; Amy Sitapati, MD[7]; Karen Lisa Smith, MD, MPH[25,*]; Mary Lou Smith, JD, MBA[26]; Hatem Soliman, MD[27,*]; Erica M. Stringer-Reasor, MD[28]; Melinda L. Telli, MD[6]; John H. Ward, MD[29,*]; Kari B. Wisinski, MD[22,*]; Jessica S. Young, MD[30]; Jennifer L. Burns[31,*]; and Rashmi Kumar, PhD[31,*]

ABSTRACT

The NCCN Guidelines for Breast Cancer include up-to-date guidelines for clinical management of patients with carcinoma in situ, invasive breast cancer, Paget disease, phyllodes tumor, inflammatory breast cancer, male 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. These NCCN Guidelines Insights focus on the most recent updates to recommendations for adjuvant systemic therapy in patients with nonmetastatic, early-stage, hormone receptor–positive, HER2-negative breast cancer.

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[1]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [2]Yale Cancer Center/Smilow Cancer Hospital; [3]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; [4]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [5]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [6]Stanford Cancer Institute; [7]UC San Diego Moores Cancer Center; [8]Dana-Farber/Brigham and Women's Cancer Center; [9]Memorial Sloan Kettering Cancer Center; [10]University of Colorado Cancer Center; [11]The University of Texas MD Anderson Cancer Center; [12]Mayo Clinic Cancer Center; [13]Fox Chase Cancer Center; [14]UCLA Jonsson Comprehensive Cancer Center; [15]Massachusetts General Hospital Cancer Center; [16]Abramson Cancer Center at the University of Pennsylvania; [17]Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; [18]Fred & Pamela Buffet Cancer Center; [19]UT Southwestern Simmons Comprehensive Cancer Center; [20]Vanderbilt-Ingram Cancer Center; [21]City of Hope National Medical Center; [22]University of Wisconsin Carbone Cancer Center; [23]University of Michigan Rogel Cancer Center; [24]UCSF Helen Diller Family Comprehensive Cancer Center; [25]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [26]Research Advocacy Network; [27]Moffitt Cancer Center; [28]O'Neal Comprehensive Cancer Center at UAB; [29]Huntsman Cancer Institute at the University of Utah; [30]Roswell Park Comprehensive Cancer Center; and [31]National Comprehensive Cancer Network.

[*]Provided content development and/or authorship assistance.

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 uponlower-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.

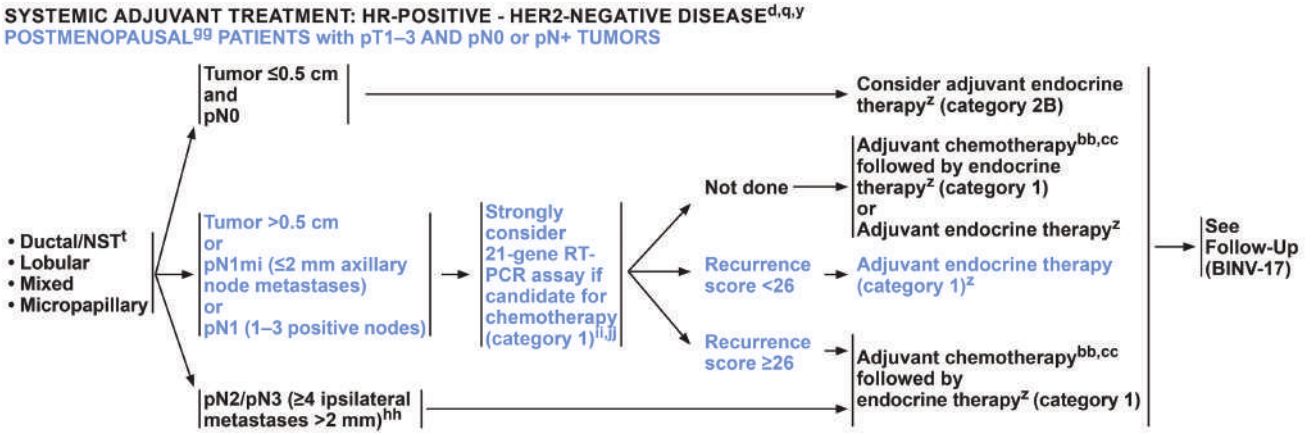
Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

The NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their application or use in any way.

The complete and most recent version of these NCCN Guidelines is available free of charge at NCCN.org.



[d] See Principles of Biomarker Testing (BINV-A).
[q] See Special Considerations for Breast Cancer in Men (Sex Assigned Male at Birth) (BINV-J).
[t] According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.
[y] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A).
[z] Consider adjuvant bisphosphonate therapy in patients with natural or induced menopause.
[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 RT is acceptable. See Adjuvant Endocrine Therapy (BINV-K) and Preoperative/Adjuvant Therapy Regimens (BINV-L).
[cc] There are limited data to make chemotherapy recommendations for those ≥70 y of age. See NCCN Guidelines for Older Adult Oncology.
[gg] See Definition of Menopause (BINV-O).
[hh] There are few data regarding the role of gene expression assays in those with ≥4 ipsilateral axillary lymph nodes. Decisions to administer adjuvant chemotherapy for this group should be based on clinical factors.
[ii] Other prognostic gene expression assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy. See Gene Expression Assays for Consideration of Adjuvant Systemic Therapy (BINV-N).
[jj] Patients with T1b tumors with low-grade histology and no lymphovascular invasion should be treated with endocrine monotherapy as the TAILORx trial did not include patients with such tumors.

BINV-6

Overview

Breast cancer is the most commonly diagnosed cancer globally and continues to be second only to lung cancer as a cause of cancer death.[1] The American Cancer Society estimates that 284,200 Americans will be diagnosed with breast cancer and 44,130 will die of the disease in the United States in 2021.[2] 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 disease, phyllodes tumor, inflammatory breast cancer, male 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.

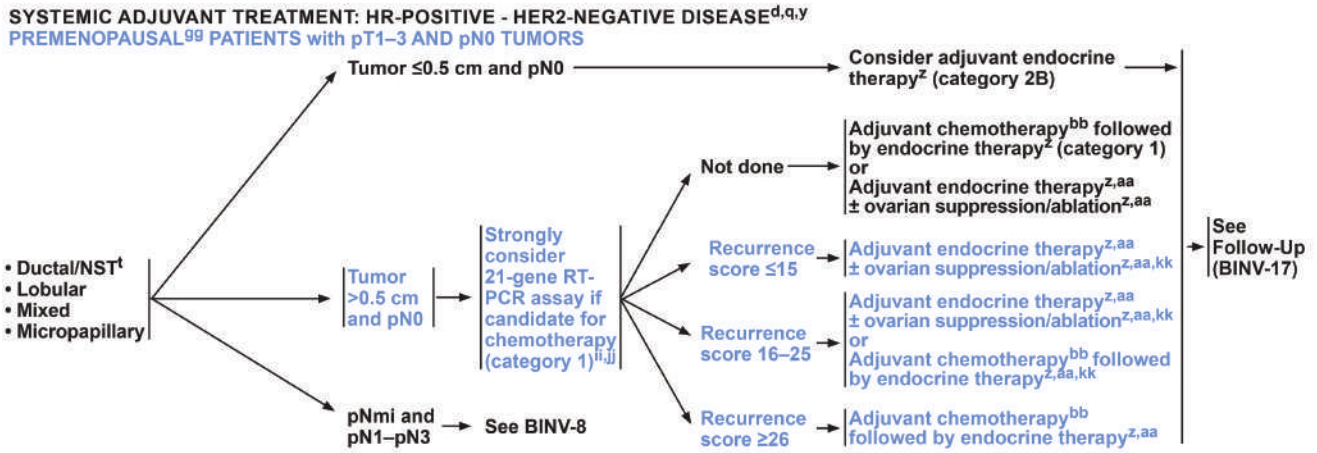
In the 2021 version of the NCCN Guidelines for Breast Cancer, the panel included updated recommendations for axillary staging; adjuvant radiation therapy; adjuvant systemic therapy for patients with hormone receptor–positive (HR+) and HER2-negative (HER2−) breast cancer; and systemic therapy for metastatic disease. This report summarizes the rationale behind the recommendations specific to adjuvant systemic therapy for patients with nonmetastatic early-stage HR+/HER2− breast cancer.

Adjuvant Systemic Therapy

In patients with early-stage breast cancer, systemic adjuvant therapy is administered to reduce risk of breast cancer recurrence. The decision is often based on individual risk of relapse and predicted sensitivity to treatment (eg, estrogen and progesterone receptors and HER2 status). The decision to use systemic adjuvant therapy requires consideration and balancing of risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of the therapy, and comorbidity. The decision-making process requires collaboration between the healthcare team and the patient.

Pathologic T1–3 HR+/HER2− Tumors

Patients with HR+/HER2− tumors receive adjuvant endocrine therapy to reduce the risk of recurrence. Those deemed at high risk for distant recurrence despite



[d] See Principles of Biomarker Testing (BINV-A).
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[t] According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.
[y] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A).
[z] Consider adjuvant bisphosphonate therapy in patients with natural or induced menopause.
[aa] Evidence suggests that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal patients with HR-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-K).
[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 RT is acceptable. See Adjuvant Endocrine Therapy (BINV-K) and Preoperative/Adjuvant Therapy Regimens (BINV-L).
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[ii] Other prognostic gene expression assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy. See Gene Expression Assays for Consideration of Adjuvant Systemic Therapy (BINV-N).
[jj] Patients with T1b tumors with low-grade histology and no lymphovascular invasion should be treated with endocrine monotherapy as the TAILORx trial did not include patients with such tumors.
[kk] In premenopausal patients with RS <26, the addition of chemotherapy to endocrine therapy was associated with a lower rate of distant recurrence compared with endocrine monotherapy, but it is unclear if the benefit was due to the ovarian suppression effects promoted by chemotherapy.

BINV-7

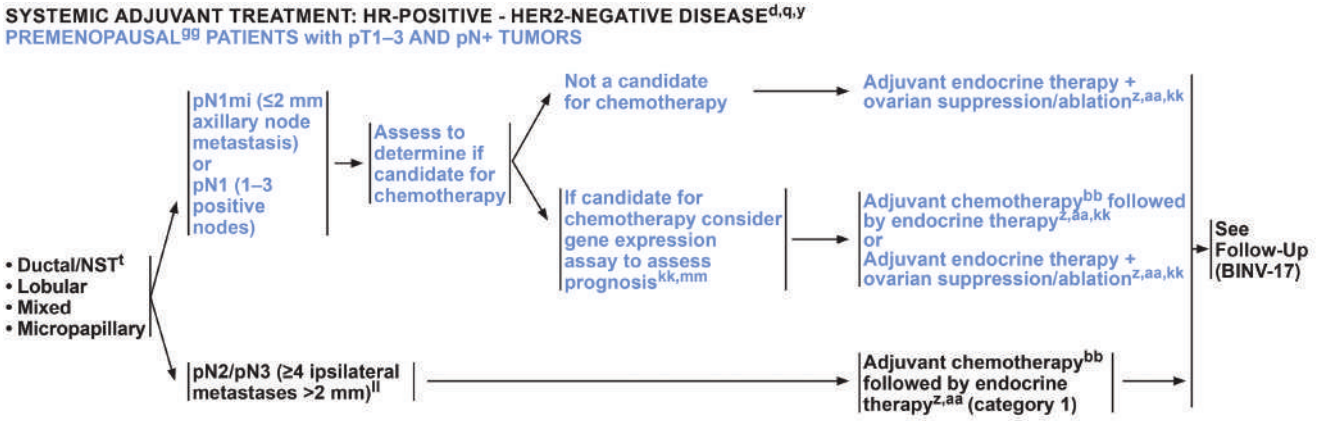
adjuvant endocrine therapy may also receive adjuvant chemotherapy. The decision whether to administer adjuvant chemotherapy in patients with HR+/HER2− tumors is based on many factors, including lymph node (LN) status, tumor size, patient age, comorbid conditions, and risk assessment based on results of a validated gene expression assay.

Among patients with pathologic T1–3 (pT1–3) HR+/HER2− tumors, on one end of the spectrum are those with small (pT1mi and T1a) and node-negative (pN0) tumors. These patients with small tumors up to 0.5 cm in greatest diameter that *do not* involve the LNs have low clinical risk of recurrence and a favorable prognosis. The incremental benefit of adding adjuvant chemotherapy to endocrine therapy in patients with such tumors is minimal.[3] On the other end of the spectrum are patients with high-risk features, such as ≥4 positive LNs. In this group, the addition of systemic chemotherapy to adjuvant endocrine therapy may play a role in reducing recurrence risk.

For patients in whom the decision whether to use chemotherapy is unclear, gene expression assays may be used to assess recurrence risk. The primary role of the gene expression assays is to determine clinical situations that warrant addition of chemotherapy to endocrine therapy to further reduce recurrence risk.

The 21-gene assay (Oncotype Dx), which determines recurrence risk using a recurrence score (RS), is one of the most validated multigene assays. The RS is helpful in determining the prognosis in patients with HR+/HER2− tumors treated with endocrine therapy alone by predicting locoregional and distant recurrence.[4–6] This assay has also been validated to predict the benefit from adding adjuvant chemotherapy to adjuvant endocrine therapy for patients with HR+/HER2− breast cancer.[7–10]

The TAILORx study evaluated outcomes in patients (n=9,719) with HR+/HER2− axillary LN-negative breast cancer.[10] At 9 years, among patients (n=1,619) with low RS (≤10), all of whom received endocrine therapy alone without chemotherapy, the rate of freedom from recurrence of breast cancer at local/regional or distant site was 96.8% and the rate of invasive disease-free survival (DFS) was 84%. Among patients (n=1,389) with a high RS (≥26), all of whom received chemotherapy, the rate of freedom from recurrence of breast cancer at local/regional or distant site was 84.8% and of invasive DFS was 75.7%.[10] The overall results from TAILORx are similar to those



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[kk] In premenopausal patients with RS <26, the addition of chemotherapy to endocrine therapy was associated with a lower rate of distant recurrence compared with endocrine monotherapy, but it is unclear if the benefit was due to the ovarian suppression effects promoted by chemotherapy.
[ll] There are few data regarding the role of gene expression assays in those with ≥4 ipsilateral axillary lymph nodes. Decisions to administer adjuvant chemotherapy for this group should be based on clinical factors.
[mm] See Gene Expression Assays for Consideration of Adjuvant Systemic Therapy (BINV-N).

BINV-8

from the West German Study Group Plan B trial[11] and NSABP B-20 trial[8] for patients with low RS and high RS. The NSABP B-20 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+ breast cancer.[8] It is important to remember that the cutoff for low, intermediate, and high RS was different in TAILORx versus NSABP B-20.

Among patients (n=6,711) with intermediate RS (11–25) in the TAILORx trial, outcomes were similar between the group that received adjuvant chemotherapy followed by endocrine therapy versus endocrine therapy alone. At 9 years, the rate of freedom from recurrence of breast cancer at distant site was 95% for those who received adjuvant chemotherapy followed by endocrine therapy versus 94.5% for those who received endocrine therapy alone; invasive DFS rates were 83.3% versus 84.3, and overall survival (OS) rates were 93.8% versus 93.9%.[10] In an exploratory subset analysis of the TAILORx trial, among patients aged ≤50 years, with an RS of 0 to 15, and receiving endocrine therapy alone, the rate of distant recurrence was 3% at 9 years. However, those with an RS of 16 to 25 had significantly lower rates of distance recurrence with the addition of adjuvant chemotherapy to endocrine therapy.[10] At 9 years, among patients with an RS of 16 to 20, the absolute difference was 3.4% lower rates of local and distant recurrences, 9% reduction in invasive DFS, and 1.6% reduction in distant recurrence in those receiving chemotherapy plus endocrine therapy. In the group with an RS of 21 to 25, the absolute difference was 8.7% lower rates of local and distant recurrence and 6.6% reduction in distant recurrence in those receiving chemotherapy in addition to endocrine therapy.[10] No benefit of chemotherapy was observed among patients aged >50 years or in the overall population. The TAILORx study did not collect data on chemotherapy-induced menopause and only 12.5% of the premenopausal patients enrolled in the trial underwent ovarian suppression.[10] A much discussed hypothesis is that chemotherapy effect may have been the result of ovarian suppression.

Results of the TAILORx trial in patients with low-risk, node-negative disease were similar to those of the MINDACT trial.[12] In the MINDACT trial, patients were stratified into clinical high- or low-risk categories using the Adjuvant! Online criteria and genomic high- or low-risk

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY[a,b]

Assay	Predictive	Prognostic	NCCN Category of Preference	NCCN Category of Evidence and Consensus	Recurrence Risk and Treatment Implications
21-gene (Oncotype Dx) (for pN0)	Yes	Yes	Preferred	1	BINV-N (2 of 5)
21-gene (Oncotype Dx) for pN1 (1–3 positive nodes)[c]	Yes	Yes	Postmenopausal: Preferred	1	BINV-N (2 of 5)
			Premenopausal: Other	2A	
70-gene (MammaPrint) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	1	BINV-N (3 of 5)
50-gene (Prosigna) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A	BINV-N (3 of 5)
12-gene (EndoPredict) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A	BINV-N (3 of 5)
Breast Cancer Index (BCI)	Predictive of benefit of extended adjuvant endocrine therapy	Yes	Other	2A	BINV-N (4 of 5)

[a] Gene expression 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 prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit is unknown.
[b] See Special Considerations for Breast Cancer in Men (Sex Assigned Male at Birth) (BINV-J).
[c] In the overall study population of the RxPONDER trial, 10.3% had high grade disease and 9.2% had 3 involved nodes.

References

categories by 70-gene assay (MammaPrint). Clinical low-risk was defined as low histologic grade and tumor size ≤3 cm, intermediate histologic grade and tumor size ≤2 cm, or high histologic grade and tumor size ≤1 cm, and clinical high-risk was defined as all other cases with known values for grade and tumor size. Patients with clinical-high/genomic-low risk were randomized to receive chemotherapy in addition to endocrine therapy or to endocrine therapy alone. At 8 years, the distant metastasis–free survival rates were 92.0% (95% CI, 89.6–93.8) versus 89.4% (95% CI, 86.8–91.5), respectively.[12] The OS at 8 years was 95.7% (95% CI, 93.9–97.0) for those receiving chemotherapy plus endocrine therapy versus 94.3% (95% CI, 92.2–95.8) for those receiving endocrine therapy alone.[12] In a subset analyses, the benefit of chemotherapy was mostly seen in patients aged <50 years. The absolute difference in distant metastasis–free survival at 8 years in those receiving chemotherapy was 5.4% ± 2.8% for patients aged ≤50 years versus 0.2% ± 2.3% for those aged >50 years.[13] It is not known whether the benefit of chemotherapy observed in premenopausal patients, in both the TAILORx and MINDACT trials, is related to chemotherapy-induced ovarian function suppression.

The RxPONDER study randomized patients (n=5,083) with HR+, pN1 (1–3 positive LNs) disease and RS ≤25 to receive adjuvant chemotherapy plus endocrine therapy or endocrine therapy alone.[14] In the overall study population, 66.8% of patients were postmenopausal and 33.2% premenopausal; 10.3% had high-grade disease; 9.2% had 3 involved nodes; and 62.6% received complete axillary node dissection and 37.4% received sentinel LN dissection. Chemotherapy and RS were both independently prognostic for invasive DFS. There was no interaction seen between RS and chemotherapy. The benefit for chemotherapy in the overall randomized cohort was 1.4% at 5 years.[14]

In a planned secondary analysis, a correlation was seen between chemotherapy benefit and menopausal status. In postmenopausal patients with RS ≤25 and pN1 (1–3 positive LNs) disease, the 5-year invasive DFS rate was 91.6% with adjuvant chemotherapy in addition to adjuvant endocrine therapy versus 91.9% with endocrine therapy alone (hazard ratio [HR], 0.97; 95% CI, 0.78–1.22), indicating no benefit from chemotherapy.[14] In the premenopausal patients with RS ≤25, the addition of adjuvant systemic chemotherapy improved outcomes. There was a 5.2% increase in invasive DFS with the addition of

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY[a,b]

Assay	Recurrence Risk	Treatment Implications
21-gene (Oncotype Dx) for postmenopausal patients with pN0 and pN1 (1–3 positive nodes)[c]	<26	Patients with T1b/c–2, pN0, HR-positive, HER2-negative tumors, with risk scores (RS) between 0–10 have a risk of distant recurrence of <4% and those with RS 11–25, derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective TAILORx study.[1] Postmenopausal patients with pT1–3, pN1, HR-positive, HER2-negative, with RS <26 derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective RxPONDER study.[2]
	≥26	In postmenopausal patients with pT1–3, HR-positive, HER2-negative, and pN0 and pN1 (1–3 positive nodes) tumors and an RS ≥26, the addition of chemotherapy to endocrine therapy is recommended.[1,2]
21-gene (Oncotype Dx) (for premenopausal patients: pN0)	≤15	Premenopausal patients with T1b/c –2, pN0, HR-positive, HER2-negative tumors with RS <16 derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective TAILORx study.[1]
	16–25	In premenopausal patients with RS between 16–25, a small benefit from the addition of chemotherapy could not be ruled out, but it is unclear if the benefit was due to the ovarian suppression effect promoted by chemotherapy in premenopausal patients.[1,2] For this group, consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either tamoxifen or an AI.
	≥26	In premenopausal patients with HR-positive, HER2-negative, and pN0 tumors and an RS ≥26, the addition of chemotherapy to endocrine therapy is recommended.[1]
21-gene (Oncotype Dx) (for premenopausal patients with 1–3 positive nodes)[c]	<26	In premenopausal patients with pT1–3 and pN1 (1–3 positive nodes) tumors and an RS <26, the addition of chemotherapy to endocrine therapy was associated with a lower rate of distant recurrence compared with endocrine monotherapy[2] but it is unclear if the benefit was due to the ovarian suppression effects promoted by chemotherapy. For this group of patients, consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either tamoxifen or an AI.[2]
	≥26	In premenopausal patients with HR-positive, HER2-negative, pT1–3 and pN1 (1–3 positive nodes) tumors and an RS ≥26, the addition of chemotherapy to endocrine therapy is recommended.[2]

[a] Gene expression 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 prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit is unknown.
[b] See Special Considerations for Breast Cancer in Men (Sex Assigned Male at Birth) (BINV-J).
[c] In the overall study population of the RxPONDER trial, 10.3% had high grade disease and 9.2% had 3 involved nodes.

References

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chemotherapy to endocrine therapy (HR, 0.45; 95% CI, 0.38–0.76),[14] and an absolute decrease in distant recurrence by 2.9% with chemotherapy. The 5-year OS was 1.3% better in chemotherapy-treated premenopausal patients (97.3 vs 98.6%; 95% CI, 0.24–0.94).[14] When further analyzed according to RS, the premenopausal patients with an RS of 0 to 13 received less absolute benefit from chemotherapy (3.9% reduction in invasive DFS) compared with those with an RS of 14 to 25 (6.2% reduction in invasive DFS). Approximately 16% of patients receiving endocrine therapy alone received ovarian suppression, compared with 4% in the chemotherapy/endocrine therapy arm.[14] However, it is also important to note that it is not clear whether the benefit seen in premenopausal patients is related to chemotherapy-induced ovarian function suppression.

Gene Expression Assays

In addition to the 21-gene assay and the 70-gene assay (MammaPrint), other gene expression assays can also provide prognostic information on outcomes with endocrine treatment, such as the 50-gene assay (Prosigna), 12-gene assay (EndoPredict), and Breast Cancer Index (BCI; HOXB13/IL17BR ratio [H/I]). None of these assays have been compared head-to-head in randomized trials and, except for the 21-gene assay, no others have been validated to predict the benefit from adding adjuvant chemotherapy to adjuvant endocrine therapy in patients with early-stage HR+/HER2− disease.

Use of gene expression assays in early-stage breast cancer continues to evolve. The clinical utility of the BCI assay was studied in the prospective phase III IDEAL trial, which randomized postmenopausal patients (n=1,824) with early-stage HR+ breast cancer to receive either 2.5 or 5 years of letrozole after completing 5 years of adjuvant endocrine therapy.[15] Patients with BCI (H/I) low demonstrated a lower risk of distant recurrence (compared with BCI [H/I] high) and no significant improvement in DFS or OS compared with the control arm with extended endocrine therapy duration.[16] Patients with T1, HR+/HER2−, pN0 tumors with BCI (H/I) high (5.1–10) demonstrated significant rates of late distant recurrence. In contrast, patients with BCI (H/I) low derived no benefit from extended adjuvant therapy.[16] These data are similar to those seen in secondary analyses of the MA.17 and Trans-aTTom studies, in which patients with HR+, T1–3, pN0 or pN+ tumors with BCI (H/I) high demonstrated significant improvements in DFS when adjuvant endocrine therapy was extended, compared with the control arm.[17,18]

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY[a,b]

Assay	Recurrence Risk	Treatment Implications
70-gene (MammaPrint) (for pN0 and 1–3 positive nodes)	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% CI, 92.5%–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, 93.1–98.1) in those who received adjuvant chemotherapy vs. 95.6 (95% CI, 92.7–97.4) in those who did not receive adjuvant chemotherapy.[3] Therefore, the additional benefit of adjuvant chemotherapy may be small in this group. In a subset analyses, the benefit of chemotherapy was mostly seen in patients under 50 years of age. The absolute difference in distant metastatic-free survival at 8 years in those receiving chemotherapy for patients ≤ 50 years was 5.4% ± 2.8% versus 0.2% ± 2.3% for those >50 years.[4] It is not known whether the benefit of chemotherapy observed in women ≤ 50 years is related to chemotherapy-induced ovarian function suppression.
	High	
50-gene (Prosigna) (for pN0 and 1–3 positive nodes)	Node negative: Low (0–40)	For patients with T1 and T2 HR-positive, HER2-negative, pN0 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.[5]
	Node negative: Intermediate (41–60)	
	Node negative: High (61–100)	
	Node positive: Low (0–40)	In patients with HR-positive, HER2-negative, pN+ tumors (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 and no distant recurrence was seen at 10 years in the TransATAC study in a similar group.[6]
	Node positive: High (41–100)	
12-gene (EndoPredict) (pN0 and 1–3 positive nodes)	Low (≤3.3)	For patients with T1 and T2 HR-positive, HER2-negative, and pN0 tumors, a 12-gene low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a–T1b,N0,M0.[7] In ABCSG 6/8, patients in the low-risk group had 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.[6,7] The assay is prognostic in endocrine and chemo-endocrine treated patients.[8]
	High (>3.3)	

[a] Gene expression 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 prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit is unknown.
[b] See Special Considerations for Breast Cancer in Men (Sex Assigned Male at Birth) (BINV-J).

References

NCCN Recommendations: pT1–3 HR+/HER2− Tumors

Patients With Tumors ≤0.5 cm and LN-Negative

The panel does not recommend adjuvant systemic chemotherapy in premenopausal or postmenopausal patients with tumors ≤0.5 cm and pN0. Adjuvant endocrine therapy alone is an option to reduce the recurrence risk. Because the benefit of adjuvant endocrine therapy in reducing the recurrence risk, particularly distant metastatic disease, is very small in this group of patients, this is a category 2B recommendation (see BINV-6 and BINV-7, pages 486 and 487, respectively).

Patients With ≥4 Positive LNs

Considering the high risk of recurrence in patients with pN2/pN3 tumors, regardless of menopausal status, the panel recommends addition of systemic adjuvant chemotherapy followed by endocrine therapy (category 1) (see BINV-6 and BINV-8, pages 486 and 488, respectively).

Patients With Tumors >0.5 cm or pN1mi or pN1 (1–3 Positive LNs)

For HR+/HER2− tumors that fall between the 2 previous extremes (>0.5 cm or either pN1mi or pN1 with 1–3 positive LNs), the panel has additionally stratified the recommendations based on menopausal status and risk assessment based on gene expression assay results. Of note, patients with pNmi disease were not studied in either the TAILORx or the RxPONDER trials.

Results from TAILORx and RxPONDER show that the 21-gene assay RS is helpful in identifying patients who can be spared adjuvant chemotherapy, especially those who are postmenopausal (or with stage pN0 and age >50 years) and have an RS ≤25, as well as patients aged ≤50 years with an RS ≤15. If a patient is a candidate for chemotherapy based on clinical characteristics, tumor stage, and pathology with a tumor >0.5 cm or with 1 to 3 involved LNs, and a multigene assay is not available or not performed to assess recurrence risk, the panel recommends systemic adjuvant chemotherapy followed by endocrine therapy (category 1). Patients who are not candidates for chemotherapy, including those with contraindications to chemotherapy or who do not wish to undergo chemotherapy treatment, gene expression assay results would not alter management, and therefore such patients may be treated with endocrine therapy alone with the consideration of ovarian ablation/suppression, if premenopausal.

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY[a,b]

Assay	Recurrence Risk/ Predictive Result	Treatment Implications
Breast Cancer Index (BCI)	BCI (H/I) Low	• For patients with T1 and T2 HR-positive, HER2-negative, and pN0 tumors, a BCI (H/I) in the low-risk range (0–5), regardless of T size, places the tumor into the same prognostic category as T1a–T1b, N0,M0. • Patients with BCI (H/I) low demonstrated a lower risk of distant recurrence (compared to BCI [H/I] high) and no significant improvement in DFS or OS compared to the control arm in terms of extending endocrine therapy duration.[9]
	BCI (H/I) High	• For patients with T1 HR-positive, HER2-negative, and pN0 tumors, a BCI (H/I) high (5.1–10) demonstrated significant rates of late distant recurrence. • In secondary analyses of the MA.17, Trans-aTTom, and IDEAL trials, patients with HR-positive, T1–T3, pN0 or pN+ who had a BCI (H/I) high demonstrated significant improvements in DFS when adjuvant endocrine therapy was extended, compared to the control arm.[9-12] • In contrast, BCI (H/I) low patients derived no benefit from extended adjuvant therapy.[9]

[a] Gene expression 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 prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit is unknown.
[b] See Special Considerations for Breast Cancer in Men (Sex Assigned Male at Birth) (BINV-J).

References

For postmenopausal patients with tumors >0.5 cm or 1 to 3 positive LNs, the panel strongly recommends considering the 21-gene RT-PCR assay to help estimate likelihood of recurrence and benefit from chemotherapy (category 1) (see BINV-6, page 486). The panel notes that although several other prognostic assays are available to estimate recurrence risk, only the 21-gene assay RS has been validated for predicting the benefit of adding adjuvant chemotherapy to further reduce the recurrence risk. Results of the RxPONDER trial show that postmenopausal patients with 1 to 3 positive LNs might not have a risk as high as previously assumed. Therefore, taking together the results of the RxPONDER and TAILORx trials, endocrine therapy alone is recommended for those with RS <26,[14,19] and based on the results of the TAILORx study, addition of adjuvant chemotherapy to adjuvant endocrine therapy is recommended for those with RS ≥26.[7,8]

For premenopausal patients, the recommendations are further stratified based on nodal status. The TAILORx analyses were performed by age and demonstrated that patients with RS ≥16 and aged ≤50 years with node-negative disease derived benefit from chemotherapy (reduction in distant recurrence) at 9 years.[19] Based on this, the NCCN panel strongly recommends considering the 21-gene RT-PCR assay to help estimate likelihood of recurrence and benefit from chemotherapy (category 1) (see BINV-7, page 487). In those with RS ≤15, the NCCN panel recommends considering endocrine therapy alone.[19] Also, patients with T1b tumors with low-grade histology should be considered for endocrine monotherapy, given that the TAILORx[19] did not include patients with such tumors.

Based on the exploratory analysis from the TAILORx study, which showed benefit of adjuvant chemotherapy in patients aged ≤50 years with an RS of 16 to 25, the panel recommends the addition of chemotherapy to adjuvant endocrine therapy or adjuvant endocrine therapy alone with or without consideration of ovarian ablation/suppression.[19] Because the TAILORx study did not collect data on chemotherapy-induced menopause and only a small portion (12.5%) of the patients on the trial underwent ovarian suppression, it remains unclear whether similar benefits could be achieved with ovarian suppression plus endocrine therapy instead of chemotherapy[20] (see BINV-7, page 487).

No randomized trial has addressed the benefit of chemotherapy for those with high RS (26–100) among

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY

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premenopausal patients with early stage, node-positive disease. Because the benefit of adjuvant chemotherapy for those with RS ≤25 is significant in the RxPONDER trial, it can be inferred that the benefit for those with RS ≥26 would be substantial.[14]

The RxPONDER results demonstrated premenopausal patients with early-stage pN1 disease and an RS of 0 to 25 derived benefit from chemotherapy[14] For patients with pN1mi (≤2 mm axillary node metastases) or pN1 (1–3 positive LNs) disease, the panel recommends assessing whether the patient is a candidate for chemotherapy based on patient factors and tumor characteristics before mandating adjuvant chemotherapy in all patients with 1 to 3 positive nodes. The decision regarding the addition of chemotherapy versus ovarian function suppression to adjuvant endocrine therapy must be individualized, and can be aided by results of gene expression assays. At this time, it is unclear whether ovarian suppression plus endocrine therapy alone will provide the same benefits as addition of chemotherapy. According to the panel, either addition of adjuvant chemotherapy to adjuvant endocrine therapy based on the RxPONDER results[14] or adjuvant endocrine therapy with ovarian ablation/suppression[20] are options for this group.

The panel has provided a list of available assays along with their treatment implications in a table on BINV-N (pages 489–493). The table was revised to include updated references for the 21-gene and BCI assays.

Summary

The updated recommendations in the NCCN Guidelines for Breast Cancer provide guidance on tailoring chemotherapy recommendations for patients with HR+/HER2− early-stage breast cancer based on clinicopathologic characteristics, menopausal status, LN status, and results of gene expression assays. Use of gene expression assays in early-stage breast cancer continues to evolve. Risk assessment using the BCI gene expression assay has also shown potential to spare certain patients from prolonged endocrine therapy.

To participate in this journal CE activity, go to https://education.nccn.org/node/89715

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