CE Case Report

# Adjuvant Chemotherapy Decisions in Clinical Practice for Early-Stage Node-Negative, Estrogen Receptor–Positive, HER2-Negative Breast Cancer: Challenges and Considerations

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**Abstract**

Decisions regarding adjuvant chemotherapy for patients with estrogen receptor (ER)–positive, HER2-negative, lymph node–negative breast cancer have traditionally relied on clinical and pathologic parameters. However, the molecular heterogeneity and the complex tumor genome demand more sophisticated approaches to the problem. Several multigene-based assays have been developed to better prognosticate the risk of recurrence and death and predict benefit of therapy in this patient population. Oncologists are often faced with the challenge of incorporating these various complex genome-based biomarkers along with the traditional biomarkers in clinical decision-making. The NCCN Clinical Practice Guidelines in Oncology for Breast Cancer are helpful in providing a general recommendation. However, uncertainty remains in the absence of definitive data for various clinical scenarios. This case report describes a postmenopausal woman with stage I breast cancer that is low-grade and ER-rich, and has an intermediate Onco*type* DX recurrence score of 28. (*JNCCN* 2013;11:246–251)

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### Learning Objectives

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

- Describe the rationale for the management methods used in this case presentation.
- Describe the ideal treatment with adjuvant chemotherapy for patients with estrogen receptor (ER)–positive HER2-negative lymph node–negative breast cancer.

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## Case Report

A 67-year-old otherwise healthy postmenopausal woman presented for adjuvant therapy recommendations after a recent mastectomy and sentinel lymph node biopsy for a stage I (pT1cN0) invasive ductal carcinoma of the left breast. Tumor size was 1.2 cm. No lymphovascular invasion or axillary lymph node involvement (0/2) was seen. The tumor was low-grade (1/3), with a low mitotic index (0.5 per high-power field) and a low proliferation index (Ki67: 5%). Biomarker studies revealed estrogen receptor–positive (ER+; Allred score: 8/8), progesterone receptor (PR)–negative (Allred score: 2/8), and HER2–negative (HER2–) expression according to immunohistochemistry. Although the tumor was low-grade and rich in ER expression, the negative PR status raised some concern because it has been associated with worse outcomes in ER+ breast cancer.[1] Given the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer recommendation to "consider" Onco*type* DX testing in this patient population[2] and the wish of the patient, we requested the test on the breast tumor. Results showed a recurrence score (RS) of 28. Because no clear guideline exists regarding chemotherapy in the intermediate-risk category when the RS is between 18 and 30, we again analyzed the traditional clinical and pathologic parameters for guidance. Based on the Adjuvant! Online model, the absolute reduction in the risk of relapse for this case is less than 2% with the first-generation chemotherapy regimen. In addition, the strong ER positivity, low tumor grade, and low proliferation index argue that the tumor is probably a luminal A–type breast cancer, a subtype unlikely to benefit from chemotherapy. The caveat is that molecular confirmation of the luminal A subtype is unavailable. After considerable discussion with the patient, the decision was made not to administer adjuvant chemotherapy. Weighing the risk/benefit ratio, it is understandable why one would not be enthusiastic about chemotherapy.

## Discussion

The role of adjuvant chemotherapy in ER+ breast cancer is heavily debated in the literature. Although the proportional risk reduction from adjuvant polychemotherapy was found to be independent of ER status and tamoxifen use in the Oxford overview,[3] the relative chemoresistance of ER+ disease has been demonstrated in the neoadjuvant setting by a consistently low pathologic complete response (pCR) rate.[4] In addition, considerably less impact on recurrence from improvement of adjuvant chemotherapy regimens was observed in ER+ compared with ER– or HER2+ disease.[5,6] The current challenge is how to accurately predict chemotherapy benefit in an individual patient. This report reviews some of the "traditional" and "novel" biomarkers as potential tools for this purpose, and Table 1 summarizes this information.

## Traditional Biomarkers

Traditional biomarkers include clinicopathologic characteristics, that are widely used in clinical practice as prognostic and predictive biomarkers, such as tumor size; nodal status; ER, PR, and HER2 status; tumor grade; and proliferation index. Several review articles have addressed their potential uses and drawbacks.[7] Low-grade, ER-rich, HER2– tumors are likely more chemoresistant, making adjuvant chemotherapy a less desirable approach. Adjuvant! Online (www.adjuvantonline.com) is a computer-based decision-making tool that integrates these traditional markers. Retrospective studies have validated this prognostic tool for clinical use, although results are less reliable in certain subgroup of patients, such as women younger than 35 to 40 years and those with additional adverse prognostic factors, such as lymphovascular invasion.[8,9] However, the limitation of the Adjuvant! Online program is the lack of consideration of ER quantification, HER2 status, and the molecular heterogeneity of ER+ disease.

## Novel Biomarkers

Progress in the molecular understanding of breast cancer and the development of sophisticated diagnostic tools has led to the availability of several multigene assays that aid in the characterization of individual tumors. Available multigene assays commonly used in clinical practice are Onco*type* DX and MammaPrint.

### Onco*type* DX

Onco*type* DX is a 21-gene reverse-transcriptase polymerase chain reaction (RT-PCR)–based assay consisting of 16 cancer-related genes involved

**Table 1 Prognostic and Predictive Biomarkers in Early-Stage Breast Cancer**

| Strength | Weakness |
|---|---|
| **Clinicopathologic Markers (Traditional Biomarkers)** | |
| ***Tumor Size and Nodal Status (Anatomic Staging)*** | |
| Most commonly used clinical variable for prognostication. | Effect of chemotherapy independent of tumor size and nodal status on EBCTCG overview. |
| Important eligibility criteria for entry into clinical trials. | Role of anatomic staging may likely diminish in the era of molecular profiling. |
| ***ER/PR/HER2 Status*** | |
| ER+ and/or PR+: strong predictor of response to endocrine therapy. | ER+ subtype is biologically heterogeneous with varying course and response to treatment. |
| HER2+: strong predictor of response to HER2-targeted therapy. | Testing by IHC is subject to high rate of discordance due to interobserver variability. |
| ASCO/CAP guidelines for IHC testing may improve the concordance rates. | |
| ***Proliferation Markers and Tumor Grade*** | |
| Generally accepted prognostic factor indicative of underlying aggressiveness of the tumor. | Not standardized, with a high degree of variability. |
| ***Adjuvant! Online*** | |
| Incorporates traditional clinicopathologic factors, such as tumor size, tumor grade, ER status, and number of positive lymph nodes. | Based on histopathologic features that are subject to interobserver variability. |
| Patient characteristics included, such as age, menopausal status, and comorbidity. | Does not incorporate ER quantification, PR status, proliferation markers, and less common histologic subtypes. |
| Provides 10-year survival estimates based on SEER registry data. | HER2 status not included. |
| Provides 10-year outcomes with chemotherapy and endocrine therapy based on EBCTCG data. | Less reliable in certain subgroups, such as patients with lymphovascular invasion and age <40 y. |
| **Gene Expression Profiling (Novel Biomarkers)** | |
| ***Multigene Assays: Oncotype DX, MammaPrint*** | |
| Oncotype DX and MammaPrint provide prognostic data in ER+ and regardless of ER status, respectively, independent of traditional clinicopathologic factors. | Investigated and validated in specific patient population. |
| Oncotype DX RS is predictive of chemotherapy benefit in ER+ breast cancer. | The role of Oncotype DX RS in predicting chemotherapy benefit in the intermediate-risk category is uncertain. |
| Pharmacoeconomic models support use of multigene assays as a decision-making tool in a managed health care setting for node-negative, ER+ breast cancer. | Data available are retrospective and results of prospective TAILORx and MINDACT clinical trials awaited. |
| ***Intrinsic Subtypes*** | |
| Subtypes have shown differences in clinical outcomes and sensitivity to chemotherapy. | Needs prospective validation. |
| PAM50 is being developed for commercial use. | Guideline needed for clinical interpretation and treatment decision-making according to intrinsic subtype and ROR score. |
| PAM50 generates ROR, which provides additional prognostic information than Oncotype DX when combined with clinical treatment score. | |
| IHC definition of intrinsic subtypes was adopted by St. Gallen Consensus Conference 2011. | |

Abbreviations: CAP, College of American Pathologists; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; ER, estrogen receptor; IHC, immunohistochemistry; PR, progesterone receptor; ROR, risk of recurrence; RS, recurrence score.

in proliferation, invasion, and ER and HER2 signaling, and 5 reference genes derived from an initial panel of 250 candidate genes published in the literature and genomic databases. The test is performed on paraffin-embedded tumor tissue and the result is reported as an RS ranging from 0 to 100 and categorized into 3 risk groups: low (RS<18), intermediate (RS 18–30), and high (RS>31). The RS provides prognostic information independent of the traditional clinicopathologic factors.[10] The prognostic utility of this test was validated in a large cohort of 668 patients with node-negative breast cancer treated with tamoxifen on the NSABP B-14 study, which showed that the 10-year distant recurrence rates for low, intermediate, and high RS were 6.8%, 14.3%, and 30.5%, respectively.[10] The role of RS in predicting chemotherapy benefit was demonstrated in a retrospective analysis of 651 patients with node-negative, ER+ breast cancers enrolled on the NSABP B20 trial randomized to tamoxifen with or without CMF/MF (methotrexate, 5-FU, +/- cyclophosphamide) chemotherapy. In this retrospective analysis, patients with a high RS derived significant benefit from adjuvant chemotherapy, with a 28% reduction in 10-year risk of relapse, whereas those with low or intermediate RS derived little benefit.[11] In the NCCN Guidelines for Breast Cancer, Onco*type* DX is a category 2B recommendation for estimating the likelihood of recurrence and chemotherapy benefit in ER+, lymph node–negative breast cancer measuring greater than 0.5 cm.[2] NCCN recommends endocrine therapy without chemotherapy for those with a low RS, and chemotherapy in addition to endocrine therapy for those with a high RS based on the data described earlier.[2] The prognostic significance of an intermediate RS is unclear and is undergoing prospective evaluation in the TAILORx study (The Trial Assigning Individualized Options for Treatment; ClinicalTrials.gov identifier: NCT00310180), in which patients with an RS of 11 to 25 are randomized to chemotherapy plus endocrine therapy versus endocrine therapy alone. A multicenter prospective study showed that results of Onco*type* DX testing significantly impacted treatment decisions among both patients and physicians.[12]

## MammaPrint

MammaPrint is a microarray-based multigene assay designed for risk assessment in patients with node-negative breast cancer regardless of ER status. The 70-gene signature consists of genes involved in proliferation, invasion, metastasis, and angiogenesis. The results are reported as a dichotomous value—low risk versus high risk of metastasis—whereas the underlying expression is a continuum.[13] This test is FDA-approved but was not widely used in the United States until recently because of the need to use frozen tumor specimens. In early 2012, MammaPrint became available for testing on paraffin-embedded tissue samples, which has made it more feasible for clinical use. The MammaPrint assay has been extensively validated in retrospective studies and is currently undergoing prospective evaluation in the MINDACT (Microarray in Node-Negative Disease May Avoid Chemotherapy; ClinicalTrials.gov identifier: NCT00433589) trial, in which patients with node-negative disease in the adjuvant treatment setting will be assessed by standard clinicopathologic prognostic factors using Adjuvant! Online and MammaPrint. Based on the recent results in node-positive patients, the MINDACT trial was amended to include patients with 1 to 3 lymph nodes.[14] Patients considered low risk on both measures will not receive chemotherapy, those who are high risk on both will receive chemotherapy, and those with discordant risk assessment will be randomized to chemotherapy or no chemotherapy.

## Intrinsic Subtypes and PAM50

Molecular classification of breast cancer based on gene expression profiling has revolutionized the understanding of breast cancer. The intrinsic subtypes of breast cancer include luminal A, luminal B, HER2-enriched, and basal-like,[15] which are associated with a different clinical course and sensitivity to chemotherapy.[16] Basal-like and HER2-enriched subgroups are associated with the highest rates of pCR to paclitaxel- and doxorubicin-containing preoperative chemotherapy compared with luminal subtypes.[16] The translation of intrinsic breast cancer subtype classification into clinical assay has been challenging because of the hierarchical clustering approach used in the original classification. The minimum set of 50 intrinsic genes (PAM50) to predict subtypes independent of hierarchical clustering has been a very encouraging development.[17] In addition to subtype prediction, PAM50 provides the risk of recurrence (ROR) score for quantitative risk assessment for relapse. The

performance of ROR score in predicting relapse-free survival and distant relapse-free survival in postmenopausal women with ER+ breast cancer treated with anastrozole or tamoxifen was compared with the performance of Oncotype DX and IHC4 for both node-negative and node-positive patients.[18] PAM50 ROR score, in conjunction with clinical treatment score (consisting of 5 clinical variables: nodal status, disease grade, tumor size, age, and treatment), provided additional prognostic information in all patient subgroups compared with Oncotype DX RS.[18] An immunohistochemistry-based approach to classifying intrinsic subtypes incorporating ER, PR, and HER2 expression and Ki-67 index was adopted by the 2011 St. Gallen Consensus Conference.[19]

## Conclusions

Management of early-stage ER+, HER2– breast cancer is undergoing remarkable changes as greater understanding of the tumor biology and molecular heterogeneity of this disease is gained. An important challenge in the path to personalized medicine is the translation of research to clinical practice and the development of treatment guidelines. As continued accumulation of prognostic and predictive biomarkers is anticipated, critical assessment is needed regarding assay validation, applicable patient population, and cost-effectiveness. Guidelines are needed for an integrated approach that incorporates various tools for clinical practice.

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## Instructions for Completion

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## Posttest Questions

1. Which of the following are intrinsic subtypes of breast cancer associate with a different clinical course and sensitivity to chemotherapy?
   a. Luminal A
   b. Luminal B
   c. HER2-enriched
   d. Basal-like
   e. All of the above
2. Which of the following are some clinicopathologic characteristics of traditional biomarkers?
   a. Tumor size
   b. Nodal status
   c. ER, PR, and HER2 status
   d. All of the above
3. True or False: Although the proportional risk reduction from adjuvant polychemotherapy was found to be independent of ER status and tamoxifen use in the Oxford overview, the relative chemoresistance of ER+ disease has been demonstrated in the neoadjuvant setting by a consistently low pathologic complete response (pCR) rate.