SUPPLEMENT

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NCCN Task Force Report: Adjuvant Therapy for Breast Cancer — Clarification and Expansion of NCCN Clinical Practice Guidelines

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This educational activity was planned and produced in accordance with ACCME Essential Areas and Policies.

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Target Audience

This educational activity is designed to meet the educational needs of physicians and other clinical professionals who manage patients with cancer.

Learning Objectives

Upon completion of this monograph, physicians should be able to:

- Explain how biologic markers such as HER2 status, quantitative estrogen receptor, or genetic markers can be incorporated as prognostic or predictive factors.
- Explain the limitations and strengths of existing risk assessment tools
- Identify the role of tamoxifen therapy in younger women
- Describe the role of aromatase inhibitors and the data supporting their use in postmenopausal women
- Discuss the use of cytotoxic chemotherapy based on risk assessment
- Summarize the role of trastuzumab in the adjuvant setting

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This publication may include the discussion of products for indications not approved by the FDA.

Participants are encouraged to consult the package inserts for updated information and changes regarding indications, dosages, and contraindications. This recommendation is particularly important with new or infrequently used products.

Activity Instructions

Participants will read all portions of this monograph, including all tables, figures, and references. A post-test and an evaluation form follow this activity, both of which require completion. To receive your continuing education certificate, you will need a score of at least 70% on the post-test. The post-test and evaluation form must be completed and returned by March 8, 2007. It should take approximately 1 hour to complete this activity as designed. There are no registration fees for this activity. Certificates will be mailed within 3 to 4 weeks of receipt of the post-test.

Supplement

NCCN Task Force Report: Adjuvant Therapy for Breast Cancer

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NCCN Breast Cancer Guidelines are also available via the Internet. For the latest update, please visit www.nccn.org.

At the beginning of each task force meeting to discuss NCCN guidelines, members disclosed financial support they have received in the form of research support, advisory committee membership, or speakers' bureau participation. Members of the task force indicated that they have received support from the following: Abraxis Oncology, Adjuvant Inc., American Cancer Society, Amgen, AstraZeneca, Abraxis, Avon Foundation, Breast Cancer Intergroup, Breast Cancer Research Foundation, Bristol-Myers Squibb, CA Breast Cancer Program, Dendreon Corporation, Department of Defense, Eli Lilly, GEM Pharmaceuticals, Genentech, Genomic Health, GHI, GIST Cancer Research Foundation, GlaxoSmithKline, MedImmune, MSABP, Nase Consortium of Breast Centers, NCI, NIH, Novartis, Novartis Japan, Ortho Biotech Oncology, Pfizer, Roche, Sanofi-Aventis, Sopherion Therapeutics, Susan G. Komen Breast Cancer Foundation, Wyeth, Xomal, and YM Bioscience Inc. Some members do not accept any support from industry. The task force did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.

Key Words

NCCN Clinical Practice Guidelines in Oncology, breast cancer, adjuvant therapy, risk of recurrence, hormone therapy, ER+, estrogen receptors, HER2, aromatase inhibitors, prognostic factors, taxanes, gene expression profiling

Abstract

The National Comprehensive Cancer Network (NCCN) first published the NCCN Breast Cancer Treatment Guidelines in 1996. The Guidelines address the treatment of all stages of breast cancer across the spectrum of patient care and have been updated yearly. Adjuvant therapy for breast cancer has undergone an especially rapid evolution over the past few years. Therefore, the NCCN Breast Cancer Guidelines Panel was supplemented by additional experts to form the Adjuvant Therapy Task Force to provide a forum for an extended discussion and expanded input to the adjuvant therapy recommendations for the Breast Cancer Treatment Guidelines. Issues discussed included methods of risk-stratification for recurrence; how biologic markers such as HER2 status, quantitative estrogen receptor, or genetic markers can be incorporated as prognostic or predictive factors; and how age, menopausal status, and estrogen receptor levels impact benefits from chemotherapy and endocrine therapy. Additionally, the task force discussed the strategies for use of aromatase inhibitors in postmenopausal women and the potential incorporation of trastuzumab into adjuvant therapy of women with HER2/*neu* positive breast cancer. This supplement summarizes the background data and ensuing discussion from the Adjvuant Task Force meeting. (*JNCCN* 2006;4[suppl 1]:S-1–S-26)

Background

The National Comprehensive Cancer Network (NCCN) first published the NCCN Breast Cancer Treatment Guidelines in 1996.[1] The Guidelines address all stages of breast cancer across the spectrum of patient care and modalities of treatment and are updated yearly.[2,3] The guidelines are developed using an evidence-driven, consensus-based process.[4]

This year, the Guidelines Panel discussion will focus on multiple issues surrounding adjuvant therapy for breast cancer, including:

- For systemic adjuvant therapy, patients are now primarily risk stratified for recurrence according to anatomic and pathologic factors, tumor size, and axillary node status, with additional consideration for tumor grade and lymphovascular invasion, with only one biologic feature, hormone receptor status, included in primary risk assessment. How can biologic markers, such as HER2/*neu* status, quantitative estrogen receptor (ER), or genomic markers be incorporated as prognostic or predictive factors?
- Can certain subsets of premenopausal women with ER-positive tumors be adequately treated using tamoxifen and/or ovarian suppression and forego adjuvant chemotherapy?

Table 1 Percentage/Year Breast Cancer-Specific Mortality Rates According to Tumor Size and Axillary Lymph NodeInvolvement

5-Year Breast Cancer-Specific Mortality Rate			
Tumor Size (cm)	0 Positive Nodes	1 to 3 Positive Nodes	More than 3 Positive Nodes
< 0.5	0.8	4.7	41.0
0.5-0.9	1.7	6.0	45.8
1.0-1.9	4.2	13.4	32.8
2.0-2.9	7.7	16.6	36.6
3.0-3.9	13.8	21.0	43.1
4.0-4.9	15.4	30.2	47.4
> 5.0	17.8	27.0	54.5

Source: Data are from SEER. Reprinted from Margoleses et al.[6]; with permission.

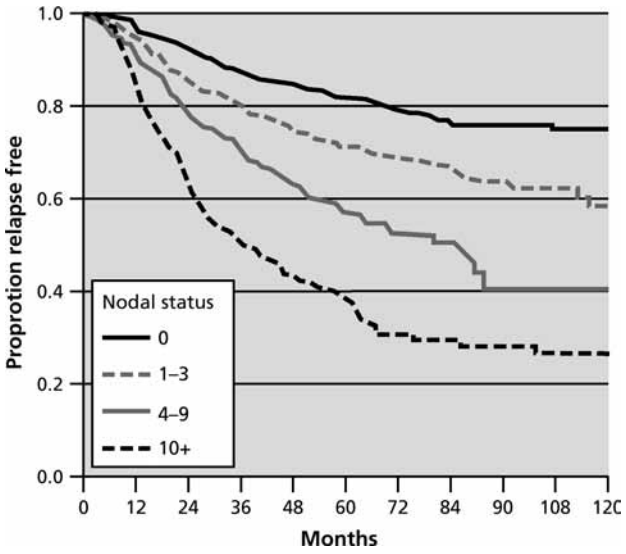


Figure 1 Relapse-free survival and number of involved lymph nodes.

- What is the optimal strategy for using aromatase inhibitors (AIs) in the adjuvant treatment of postmenopausal women with ER+ breast cancer?
- What is the role of trastuzumab in the adjuvant treatment of women with HER2/*neu* overexpressing breast cancer?
- How does age impact the value of adjuvant systemic therapy?

This Supplement summarizes the background data and ensuing discussion presented at the NCCN Adjvuant Therapy Task Force meeting.

Stratification for Risk and Benefits of Adjuvant Therapy, Prognostic and Predictive Factors

Anatomic- and Pathologic-Based Prognostic Factors

Tumor Size: Tumor size is a well-established independent prognostic factor for breast cancer, with the risk of relapse increasing as tumor size increases, regardless of axillary lymph node status (Table 1).[5,6] Recent Surveillance, Epidemiology, and End Results (SEER) Program data provide additional information on the relationship between tumor size and overall survival.[7] For the time period of 1995-1999, women with axillary lymph node–negative breast cancers with tumors less than 1 cm had a 5-year relative survival rate of 100%, whereas those with axillary lymph node–negative breast cancers with tumors 5 cm or greater had a 5-year relative survival of 81%.[7] Similarly, in women with axillary lymph node–positive breast cancer, those with tumors less than 1 cm had a 5-year relative survival of 92.6% compared with 62.9% for those with tumors 5 cm or greater, uncorrected for number of positive axillary lymph nodes. A significant 5-year overall survival difference has also been seen between axillary lymph node–negative tumors 5 mm or less (91%) and those 6 to 10 mm (75%) (P = .0001).[8] Most of the difference in survival between patients with the T1a (5 mm or less) and T1b (6–10 mm) tumors is caused by the greater probability of death from causes other than breast cancer in the group with larger tumors. The reasons for these results are uncertain but may be related to biases as to which patients are diagnosed with small tumors (< 5 mm).

Nodal Status: Survival and recurrence of breast cancer are related most strongly to the number of positive axillary lymph nodes. Patients with axillary lymph node–negative disease have a 72% survival rate and 19% recurrence rate at 5 years, compared with a 63% survival rate and 33% recurrence rate for patients with 2 positive lymph nodes.[9] Each additional positive lymph node involved at the time of diagnosis is associated with increased recurrence and decreased survival rates, at least up to 10 involved axillary lymph nodes. The impact of positive axillary lymph nodes is also evident, even in patients with tumors smaller than 0.5 cm; those with tumors less than 0.5 cm and axillary lymph node–negative disease have a 0.8% 5-year breast cancer-specific mortality rate compared with 4.7% for patients with 1 to 3 positive axillary lymph nodes and 41% for those with 4 or more positive axillary lymph nodes (Table 1).[6]

The American Joint Committee on Cancer (AJCC) pathologic staging system for breast cancer now reflects the impact of number of positive axillary lymph nodes on prognosis. Pathologic N1 disease is defined as from 1 to 3 positive nodes; N2 from 4 to 9 positive nodes, and N3 as 10 or more positive nodes. As seen in , relapse-free survival is strongly impacted by axillary nodal status. Additionally, the survival curves never completely flatten, even after 20 years of follow up, indicating about a 4% annual relative risk of recurrence. Patients with many positive lymph nodes tend to experience recurrence within 3 to 5 years. The curves start to flatten as the risk of recurrence decreases in patients who do not experience recurrence within

5 years. However, the risk of recurrence continues for decades.[10,11]

***Tumor Histology and Grade*:** Ductal, lobular, mixed, and medullary histologies are considered "usual risk" breast cancers, and tubular, mucinous (colloid), cribriform, papillary, adenoid cystic, and colloid histologies are considered favorable. "Usual risk" implies that the histologic impact is similar to that of the usual ductal or lobular breast cancer not otherwise specified. The general statistics regarding the probability of recurrence or death from breast cancer are based on the usual risk histologies. Fewer data are available on the favorable histologies, in part because of their relative rarity. However, a tumor with a predominantly tubular histology (at least 90%) is associated with a good prognosis because it rarely spreads to the axillary nodes, whereas a mucinous tumor is associated with a good prognosis because its size is related to the abundance of mucinous material rather than malignant cells.[12] Poor prognostic tumors include those with micropapillary and metaplastic histologies. In the current guidelines, lymphovascular invasion is also listed as an unfavorable histologic characteristic that would prompt consideration of adjuvant therapy even in patients with node–negative tumors less than 1 cm in diameter. This recommendation is based on data documenting that, independent of node–negative disease, lymphovascular invasion is associated with an increased risk of locoregional recurrence and death from breast cancer.[13]

***Minimal Residual Disease*:** Assessment of minimal residual disease, as evidenced by immunohistochemical or polymerase chain reaction (PCR)-based detection of epithelial cells in bone marrow samples, has been used as a prognostic factor, primarily in Europe. Minimal residual disease persists despite adjuvant therapy in many patients with breast cancer for up to 4 years after surgery.[14] Reports on the prognostic value of minimal residual disease detection show conflicting results. In a systematic review of published studies, minimal residual disease, as detected with immunohistochemistry, was associated with the expression of ER, larger tumor size, higher histologic grade, and 3 or more positive axillary lymph nodes.[15] At 5 years' follow up, immunohistochemical positivity was associated with lower disease-free survival (DFS). However, it is not yet known whether minimal residual disease is an independent predictor for recurrence or death. At present, the NCCN guidelines do not recommend assessment of minimal residual disease as a necessary component of staging, treatment, or follow-up.

Gene Expression as a Prognostic and Predictive Tool

Gene expression using either gene microarray techniques or reverse transcriptase-PCR may provide prognostic information that complements conventional factors such as tumor size, hormone-receptor, nodal status, and tumor grade, and in some cases may do so with more precision and/or reproducibility. Gene microarrays consist of DNA sequences complementary to the sequences of interest that are arrayed on a solid surface. For example, van't Veer et al.[16] studied 78 lymph node–negative sporadic breast cancers from patients younger than 55 years at diagnosis with the goal of identifying a prognostic gene expression signature. RNA was isolated from fresh-frozen tumor tissue and tested on microarrays containing approximately 25,000 human genes. The investigators looked for genes that were significantly different across samples. The resulting 5,000 genes were further narrowed to a 70-gene prognostic signature. This training set outperformed all clinical variables in predicting the likelihood of distant metastases within 5 years in this group of women younger than 55 years of age and with lymph node–negative breast cancer.

A subsequent validation study was conducted in 295 consecutively treated patients younger than 53 years of age whose tumors were stored fresh-frozen in the tissue bank of the Netherlands Cancer Institute.[17] Ten of 151 node–negative patients received adjuvant therapy, and 120 of 144 node–positive patients received adjuvant therapy. With a median follow up of 6.7 years, patients with a good-prognosis genetic signature showed an 85% and poor-prognosis genetic signature showed a 51% 10-year distant metastases-free survival (log-rank $P < .001$; Figure 2) Patients with a good-prognosis genetic signature showed a 95% 10-year overall survival compared with 55% for those with a poor-prognosis genetic signature (log-rank $P < .001$). The same discrimination was apparent when patients were subdivided into node–positive and -negative groups. However, whether patients under age 53 years would be willing to forego adjuvant therapy if the metastases-free survival was only 85% is uncertain. Further, the young age of the patients in this study make it uncertain if the results apply to those 53 years or older. In a multivariate analysis of other common prognostic factors, genetic signature remained significant. Additionally, genetic signatures separated

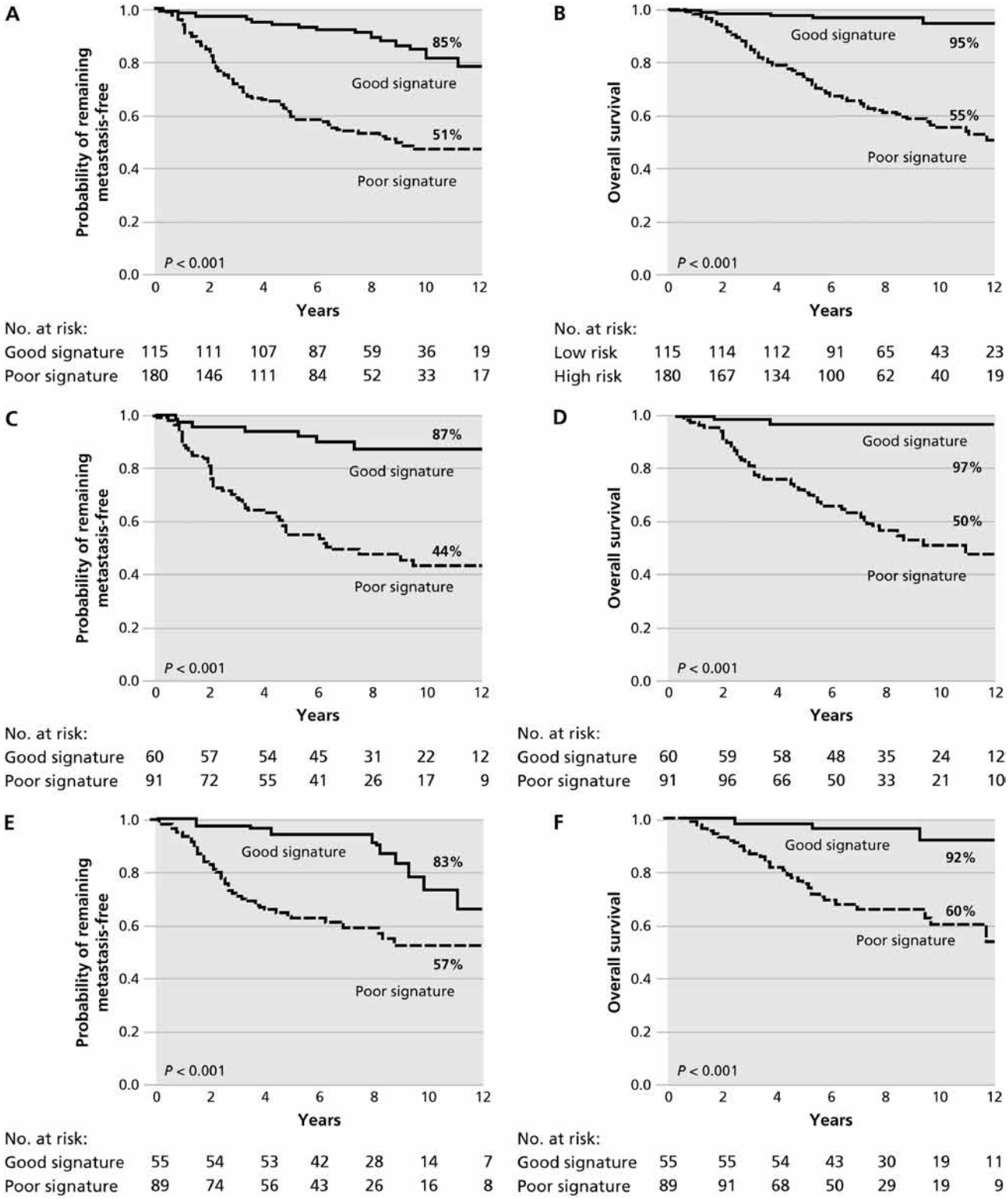


Figure 2 Kaplan-Meier analysis of the provability that patients would remain free of distant metastases and the probability of overall survival among all patients (A and B, respectively), patients with lymph-node-negative (C and D, respectively), and patients with lymph-node-positive disease (E and F, respectively) according to whether they had a good-prognosis or poor-prognosis signature. The P values were calculated with the use of the log-rank test.

Source: Reprinted with permission from Van de Vijer et al.[17]

high and low risk better than the St. Gallen or NIH classifications, which are based on currently used prognostic factors.

The European Organization for the Research and Treatment of Cancer (EORTC) has begun a trial of patients under age 55 with early stage breast cancer. Patients will be randomized to undergo risk assessment based on traditional clinical and pathologic factors or based on the 70-gene array. Patients considered at low risk based on either clinical assessment or gene array will receive either endocrine therapy or no therapy. Those considered at average or high risk will receive either chemotherapy or combined chemo-hormonal therapy. The investigators predict that 27% more patients will be considered at low risk using the gene array than using traditional factors.

One of the limitations of using the gene microarray technique is that it requires fresh or frozen tissue. In contrast, the RT-PCR technique can be performed on formalin-fixed tissue; this technique has been primarily investigated in the United States. To develop one commercially available RT-PCR technique, the Oncotype DX assay, about 250 candidate genes were selected for further testing based on microarray data, data from the literature, and data from genomic databases. These 250 candidate cancer genes were tested in 3 different data sets to identify genes of interest in terms of prognostic discrimination.[18–20] Using the results of these 3 data sets, 16 genes were identified as strongly associated with recurrence, and 5 additional reference genes were also included (Figure 3) An algorithm was developed to quantify risk for distant recurrence based on expression of these genes (21-gene recurrence score). The recurrence score is expressed on a scale from 0 to 100, and patients are classified as low risk if they have a recurrence score of less than 18, intermediate risk for scores between 18 and 30, and high risk for scores of 31 or higher.

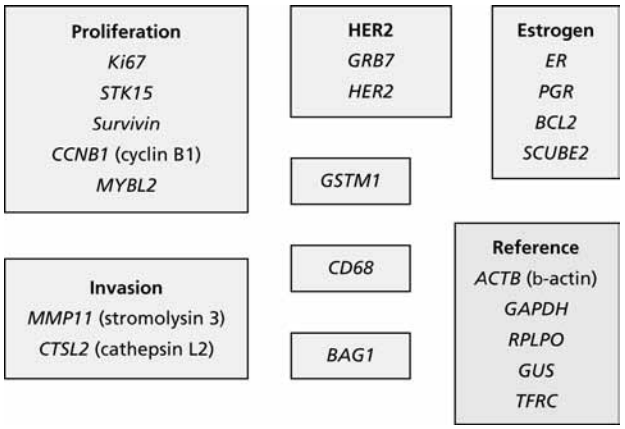


Figure 3 The 21-gene panel of the Oncotype DX™ assay from Genomic Health, Inc. Genes are grouped on the basis of function, correlated expression, or both. The *GRB7, ER,* proliferation, and invasion group scores are calculated from individual gene-expression measurements, as follows: *GRB7* group score = 0.9 x *GRB7* + 0.1 × *HER2* (if the result is less than 8, then the *GRB7* group score is considered 8); *ER* group score = (0.8 × *ER* + 1.2 x *PGR* + *BCL2* + *SCUBE2*) ÷ 4; proliferation group score = (*Survivin* + *KI67* + *MYBL2* + *CCNB1* [the gene encoding cyclin B1] + *STK15*) ÷ 5 (if the result is less than 6.5, then the proliferation group score is considered 6.5); and invasion group score = (*CTSL2* [the gene encoding cathepsin L2] + *MMP11* [the gene encoding stromolysin 3]) ÷ 2. The unscaled recurrence score (RSU) is calculated as RSU = + 0.47 × *GRB7* group score - 0.34 × *ER* group score + 1.04 x proliferation group score + 0.10 × invasion group score + 0.05 × *CD68* − 0.08 × *GSTM1* − 0.07 × *BAG1*. The recurrence score (RS) is rescaled from the unscaled recurrence score, as follows: RS = 0 if RSU < 0; RS = 20 × (RSU - 6.7) if 0 ≤ RSU ≤ 100; and RS = 100 if RSU > 100. Cutoff points classify patients into the following categories: low risk (recurrence score, less than 18), intermediate risk (recurrence score, 18 but <31), and high risk (recurrence score, 31 or higher). *Source:* Reprinted with permission from Paik et al.[21]

To validate the prognostic ability of the 21-gene recurrence score on risk of distant recurrence, the test was evaluated in an independent set of samples from patients in the NSABP B-14 trial (node–negative, ER-positive breast cancer treated with tamoxifen).[21] The main objective of the validation study was to determine whether patients with a low recurrence score had a statistically significantly better outcome than those with a high recurrence score. Analysis showed that patients with a low-risk recurrence score (51% of patients) had a 6.8% risk of distant recurrence at 10-years follow up compared with 14.3% and 30.5% for those with intermediate- and high-risk scores, respectively.

Additionally, recurrence score was a significant predictor of recurrence independent of age, tumor size, and tumor grade, although these factors retained some prognostic value based on their hazard ratio in the proportional hazards model. Recurrence score was found to be a continuous predictor of outcome, so that cutoff values for different risk categories are somewhat arbitrary. In a subset analysis according to different age, tumor size, and tumor grade categories, recurrence score was a significant predictor in all subgroups, although some analyses included small numbers of patients, with resulting wide confidence intervals.

Habel et al.[22] also reported on a nested case-control study of the 21-gene recurrence score. The community-based population was derived from all node–negative breast cancer patients (< 75 years) diagnosed from

1985 to 1994 at 14 Northern California Kaiser hospitals who had not been treated with adjuvant chemotherapy. The results of the study showed that the 21-gene RT-PCR recurrence score was both prognostic for recurrence and predictive for tamoxifen benefit in patients with node–negative, ER-positive breast cancer treated with tamoxifen.

Besides these specific genomic markers, conventional risk stratification has also incorporated additional pathologic and biologic factors. For example, the NCCN guidelines also recommend stratification according to HER2 status and angiolymphatic invasion. Quantitative ER status, historically a routine part of breast tumor evaluation, is reappearing as a marker of risk. One challenge is to assess how independent these tests are of one another. For instance, if a tumor is truly HER2 overexpressing, it is essentially impossible for it to have a low risk score as judged by the 21-gene Oncotype DX assay.

Additionally, the 21-gene recurrence scores can be compared with computer-based algorithms. For example, Bryant et al.[23] compared risk stratification using recurrence score and *Adjuvant! Online*. Using the 668 patients from the NASBP-B14 validation study, *Adjuvant! Online* was used to estimate breast cancer–specific mortality. Cutoffs were selected so that patients were categorized into low, intermediate, and high risk for recurrence with a similar distribution as that based on recurrence score. Thus, per design, both systems categorized similar percentages of patients as having low, intermediate, and high risk. However, only 48% of patients were classified in the same category by both systems. Both systems, independent of each other, were significant predictors of time to distant recurrence, although recurrence score resulted in a slightly better discrimination.

Current use of the 21-gene recurrence score as a prognostic factor should be limited to patients with node–negative, ER-positive tumors treated with endocrine therapy. Evaluating the recurrence score as a prognostic factor is likely to be even more challenging in patients with node–positive disease, because recurrence score will probably have a different impact according to the number of positive nodes.

Although initial data regarding the 21-gene recurrence score as a prognostic factor are promising, there are limitations. Data analysis is based on stored tissue from breast cancers excised almost 20 years ago. The recurrence score has not been adequately evaluated for small breast tumors (0.1–0.6 cm). Clinical experience with recurrence score is still limited, and technical problems with the test may become more apparent as experience accumulates.

Genetic Expression as a Predictive Factor

Another potential application of the use of genetic marker techniques is the potential to predict benefit from adjuvant endocrine or chemotherapy. For example, although predictive factors exist for response to endocrine therapy and trastuzumab therapy, clinicians currently lack predictive factors for response to chemotherapy. Evidence is accumulating that cancer biology plays an important role regarding benefit from chemotherapy in axillary lymph node–positive disease. This evidence is particularly important for postmenopausal patients with node–positive disease, for whom the value of chemotherapy is less certain.

For example, analysis of proliferative genes might be most predictive of response to chemotherapy, estrogen-related genes might predict an endocrine therapy benefit, and HER2/*neu* overexpression might relate to SERM resistance and also to benefit from anthracycline-based chemotherapy. Gianni et al.[24] correlated the RT-PCR recurrence score with the likelihood of pathologic complete response (pCR) in 89 patients receiving neoadjuvant chemotherapy. Pathologic CR was more likely among patients with tumors with a high recurrence score. Whether this same result could have been predicted with a quantitative analysis of estrogen and progesterone receptor (PR) is unknown. In an abstract by Paik et al.,[25] the 21-gene recurrence score was used to determine benefit from tamoxifen in the NSABP-B14 trial. Regression analysis indicated that the recurrence score quantifies the likelihood of distant recurrence because it captures both prognosis and response to tamoxifen. Benefit was seen from tamoxifen versus placebo in patients with low or intermediate recurrence scores but no apparent benefit was seen for patients with high recurrence score.

The second part of this study focused on patients participating in the NSABP-20 trial (tamoxifen plus chemotherapy vs. tamoxifen alone in patients with axillary lymph node–negative, ER-positive breast cancer), which showed an overall benefit for combined therapy. Patients with low recurrence score derived minimal if any benefit from chemotherapy. Patients with intermediate recurrence score also received minimal if any benefit from chemotherapy, but because

of the small number of patients in this subgroup, a modest benefit cannot be excluded. Conversely, patients with high recurrence score had a large absolute benefit from the addition of chemotherapy (28% absolute increase in distant DFS).

Age as a Prognostic and Predictive Factor

The role of age (both young and old) as both an independent or surrogate prognostic and predictive factor is controversial. Whether age is a surrogate for the interaction of host and tumor biologic features commonly present in specific age groups is increasingly questioned. Examples include age-related effects of chemotherapy on ovarian function and increasing prevalence of ER-positive disease with increasing age. Tumors in young women often have higher tumor grade, mitotic rate, lymphatic vascular invasion, and less ER/PR expression than those in older women.[26] The role of adjuvant endocrine therapy in premenopausal women is confounded by the inaccuracy of ER testing in some studies and the resulting inclusion of patients with ER-negative disease, the limited use of tamoxifen in early premenopausal studies, and the confounding indirect endocrine effects of chemotherapy. At the other end of the spectrum, older patients are more likely to present with multiple chronic conditions that may impact life expectancy more than the diagnosis of breast cancer and decrease the absolute benefits from therapies providing substantial relative risk reductions from breast cancer.[27]

The Early Breast Cancer Trialists' overview analysis documented that women with ER-positive breast cancer benefit from adjuvant tamoxifen by a reduction in the annual odds of recurrence or death relatively consistently across all age groups.[11] In contrast, the reduction in the annual odds of recurrence or death conferred by adjuvant polychemotherapy decreased with increasing age (Table 2).

The International Breast Cancer Study Group (IBCSG) presented 10-year disease-free and overall survival data according to age (older or younger than 35 years) for patients who received CMF adjuvant therapy in the premenopausal or perimenopausal setting.[28] The 10-year DFS was 47% in the older group compared with 35% in the younger group ($P < .001$). Although 10-year DFS rates were not markedly different in older patients based on ER+ or ER− disease (45% vs. 46%; $P = .27$), the younger group showed a significantly worse DFS in patients with ER+ than in those with ER− tumors (25% vs. 47%, respectively; $P = .014$). Because differences by age were seen in the proportion of women experiencing amenorrhea, the impact of chemotherapy on endogenous estrogen and/or progesterone production may be related to the observed differences in DFS by age and hormone receptor status. The importance of age and ER status on prognosis has been confirmed in other studies.[29]

Table 2 Reductions in Recurrence and Death From Breast Cancer With Polychemotherapy

Age at Diagnosis	Ratio of Annual Events, Recurrence (SE)	Ratio of Annual Events, Death (SE)
<40 years	0.60 (0.06)	0.71 (0.07)
40-49 years	0.64 (0.04)	0.70 (0.05)
50-59 years	0.77 (0.03)	0.85 (0.04)
60-69 years	0.87 (0.03)	0.91 (0.04)
70+ years	0.88 (0.11)	0.87 (0.12)

Source: Data are reprinted from Early Breast Cancer Trialists Collaborative Group[11]; with permission.

In a similar IBCSG database of women treated with CMF for 3 to 9 courses, 88% of those younger than 35 years had persistent menses compared with only 34% in those 35 years or older.[29] Although the numbers in these subgroups do not produce robust statistics, persistent menses in premenopausal women with ER-positive disease emerges as an increased relative risk factor of recurrence not seen with ER–negative tumors. NSABP-B13 randomized women with node–negative disease to receive either methotrexate and fluorouracil (MF) or no adjuvant therapy.[30] Among those with ER-negative tumors, relative risk of recurrence was the same above and below age of 35 years, suggesting no impact of amenorrhea on the benefit of chemotherapy in women with ER-negative tumors. These results highlight the importance of endocrine therapy for young premenopausal patients with ER-positive disease, women who are likely to continue menstruating after adjuvant chemotherapy, and who often must deal with family planning issues if they are to defer pregnancy for 5 years to complete adjuvant endocrine therapy.

Recommendations relating to the use of adjuvant therapy for women over the age of 65 years are hindered because although the median age of a patient with breast cancer is 65 years, the older age group is under-represented in clinical studies. Review of

4 randomized trials recruiting women with lymph node–positive disease between 1975 and 1999 revealed that only 8% of the participating patients were over 65 years and only 2% were over 70 years.[31] This is particularly concerning because the study noted that older women showed similar reductions in breast cancer mortality and recurrence and that, although tolerance was not exactly the same between older and younger patients, therapy was generally well tolerated in all age groups. Whether the tolerability of chemotherapy in the older patients in this study is because of patient selection favoring more vigorous older patients remains unknown.

Data from the NCCN database from 1997 to 2001 showed that the percentage of patients over the age of 70 participating in clinical trials was only 11%. One reason for the poor accrual of older women is that randomized trials in this country have focused on of chemotherapy, which may not be of great interest to older women; in Europe, trials focusing on endocrine therapies had better accrual in the older group. Surveys have suggested that older age (> 70 years) is considered a barrier to participation in clinical trials.[32] This is particularly true for physicians, who less frequently offer clinical trials to older patients, perhaps because of the challenge of explaining the intricacies of a clinical trial to the elderly.[33,34] However, the emergence of better prognostic and predictive factors may make recruiting older patients into trials easier. Also, with the size of breast cancers declining because of earlier detection, future trials may focus on ways to offer less therapy, which may appeal more to older women.

Clinical trials focusing on postmenopausal patients have shown that adjuvant chemotherapy is effective in specific subsets of patients. For example, IBCSG-IX studied tamoxifen with or without 3 cycles of CMF in true postmenopausal patients with node–negative disease.[35] Chemotherapy benefit was limited to those with ER-negative disease (n = 382; 5-year DFS, 84% vs. 69%; P = .003; 5-year overall survival, 89% vs. 81%; P = .01); no benefit was seen with ER-positive disease (n = 1,217; 5-year DFS, 84% vs. 85%; P = .92; 5-year overall survival, 95% vs. 93%; P = .80). However, only 28% of participants were older than 65.

NSABP B-20 randomized women with ER-positive breast cancer to tamoxifen, tamoxifen plus CMF chemotherapy, or tamoxifen plus methotrexate/5-fluorouracil/leucovorin chemotherapy.[30] Analysis of NSABP B-20 stratifying women 49 years of age and younger versus 50 years of age or older documented benefits in DFS and overall survival regardless of age. A more recent analysis stratified patients enrolled in this trial to receive either tamoxifen or tamoxifen plus CMF as 49 years or younger, 50 to 59 years, or 60 years or older. In this analysis, at 12-years CMFT was superior to tamoxifen alone in women 49 years or younger (DFS, 76% vs. 89%; overall survival, 84% vs. 90%) and in women 50 to 59 years of age (DFS, 78% vs. 88%; overall survival, 84% vs. 90%), but not in those age 60 years or older (DFS, 85% vs. 89%; overall survival, 81% vs. 77%).[36]

Clinical trial SWOG 8814 involved postmenopausal patients with hormone receptor-positive, node–positive breast cancer who were randomized to receive tamoxifen alone, tamoxifen begun concurrent with CAF chemotherapy, or tamoxifen begun after completion of CAF chemotherapy. The results showed a DFS and overall survival benefit from chemotherapy, suggesting that chemotherapy, including an anthracycline regimen, could be considered in older patients. To date, potential interactions between age and DFS or overall survival in this study have not yet been reported.[37]

The practice of grouping all postmenopausal women together in a single subset assumes that the biology of breast cancer does not differ by age group. Gennari et al.[38] categorized 2,999 consecutive postmenopausal patients referred for breast cancer surgery as "young postmenopausal" (50–64 years), "older postmenopausal" (64-75 years), or "elderly postmenopausal" (≥76 years). Compared with the young postmenopausal, elderly patients had a higher degree of ER or PR positivity in their breast cancers (54.9% vs. 39.7%), less vascular invasion (24.6% vs. 30.6%), less HER2 expression (32.7% vs. 40.8%), and more comorbidities (21.9% vs. 10.5%). Thus, differences across age groups may reflect a complex interrelationship among host factors, tumor prognostic factors, and therapy factors. Potential host factors include individual pharmacogenetic profile, comorbidities, and frailty. In this context, comorbidity must be viewed as a risk factor for frailty, while disability is an outcome of frailty.[39] Life expectancy and resulting limitation in potential benefits over time should also be considered. The life expectancy for an average 65-year-old women in the United States is 20 years, which declines to 13 and 7 years at 75 and 85 years, respectively.[40] Therapy factors include the choice of endocrine therapy, chemotherapy regimen, or biologic therapy. Tumor factors include conventional prognostic

factors and emerging factors such as gene expression profiles. Initial criterion for adjuvant treatment options should not focus on chronologic age alone, but also on tumor biology and patient preference.

Decision-Making Tools

Physicians provide widely varying estimates of DFS associated with observation or adjuvant therapy in different clinical situations.[41] *Numeracy* and *Adjuvant! Online* are Internet-based tools developed to improve and facilitate the use of accurate prognostic and predictive estimates when considering adjuvant chemotherapy and endocrine therapy. Both tools became publicly available in 2001, although *Adjuvant!* had been available earlier.[42,43] *Numeracy* was based on initial estimates of baseline prognosis developed from expert opinion and updated with proportional reductions of risk recurrence based on clinical trials.[44] *Adjuvant! Online* is more evidence-based, with estimates of prognosis developed from SEER data and allows for consideration of comorbidity and competing causes of death.[45] At publication time, *Numeracy* is no longer available. *Adjuvant! Online* is available both on the internet and in a form downloadable to PDAs (www.adjuvantonline.com).

Adjuvant! Online uses a complex algorithm that draws on numerous patient- and tumor-related variables and allows the oncologist to enter additional information. *Adjuvant!* also provides additional information on a wide variety of adjuvant therapies, categorized as first-, second-, or third-generation. Based on patient characteristics, the tool provides proportional risk reductions associated with different options. Extensive help files detail the evidence used to make prognostic and efficacy estimates. Guideline information and medical illustrations detailing surgical, radiation, and adjuvant therapy issues are included, and links to clinical trial organizations are also available.

Adjuvant! Online includes a prognostic factor impact calculator that allows the user to add additional prognostic information, supplying information about what independent relative risk is conferred. The information is presented in several languages in a format designed to be used in physician-patient discussions. For example, women considering no additional therapy can see, based on individual characteristics, how many women with similar characteristics would be alive if the considered adjuvant therapy were added.

Adjuvant! Online was independently validated based on the British Columbia Breast Cancer Outcomes Unit.[46] Demographic, pathologic, staging, and treatment data for 4,083 women with early breast cancer were entered into *Adjuvant! Online* to calculate predicted overall and cancer-specific survival for each patient, and the information was compared with outcomes in the database. Predicted and observed outcomes were within 2% for most subgroups.

Although the tool is designed to be internally consistent, the generated estimates depend on the available datasets, which are imperfect. For example, disease classified as node–negative as staged using sentinel node biopsy is assumed to carry the same prognosis as that staged using formal axillary dissection. Although this seems reasonable, definitive data showing this is not yet available. Lack of long-term data about widely used adjuvant therapies presents another uncertainty. The program deals with these uncertainties by showing how estimates were made and allowing the user to enter other estimates.

Tools such as *Adjuvant* can be used in a variety of ways. However, both patients and physicians must be aware of the limitations. It is a supplement to informed decision-making but does not substitute for clinical judgment or good communication.

Endocrine Therapy

Tamoxifen in the Premenopausal and Postmenopausal Setting

For more than 2 decades after its introduction, tamoxifen was the gold standard for adjuvant hormonal therapy in patients with early stage ER-positive breast cancer. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published a sequential series of overview analyses (meta-analyses) addressing the use of tamoxifen as an adjuvant therapy[11] (Table 3). The overview analysis documented the benefits of tamoxifen in reduction in annual odds of recurrence and of death in women with ER-positive or -unknown breast cancer, with increasing benefits shown with increasing duration of tamoxifen use up to 5-years of therapy. These benefits are consistent across all age groups, regardless of axillary lymph node involvement or not, and regardless of whether or not cytotoxic chemotherapy is administered or not.

Based on results of the overview analysis and the NSABP B-14 trial, treatment with tamoxifen is

Table 3 Overview Analysis Regarding Tamoxifen as Adjuvant Therapy

	Reduction in Annual Odds of Recurrence (SE)	Reduction in Annual Odds of Death (SE)
By ER status, 5-years tamoxifen		
ER-negative	-4% (7)	-4% (8)
ER-positive	41% (3)	34% (4)
ER-unknown	31% (7)	20% (9)
Duration of treatment ER-positive only		
1-2 years	26% (3)	18% (3)
5 years	41% (3)	34% (4)
By age ER-positive or unknown		
<40 years	44% (10)	39% (12)
40-49 years	29% (7)	24% (9)
50-59 years	34% (5)	24% (7)
60-69 years	45% (5)	35% (6)
70+ years	51% (12)	37% (15)
By chemotherapy		
No polychemotherapy	41% (3)	31% (4)
Polychemotherapy + concurrent tamoxifen	40% (8)	39% (9)
Polychemotherapy + sequential tamoxifen	31% (7)	24% (10)

generally for 5 years. In the NSABP B-14 trial, patients completing 5 years of tamoxifen were randomized to stop tamoxifen or to complete 10 years of tamoxifen therapy.[47] Those randomized to 10-years of tamoxifen experienced a significant reduction in DFS (78% vs. 82% at 7 years; $P = .03$) and overall survival (91% vs. 94% at 7 years; $P = .13$) compared with 5 years of tamoxifen. Although the trial only involved patients with node–negative disease, the 5-year recommendation was extended to those with node–positive disease. Other clinical trials have found no benefit to durations of tamoxifen over 5 years.[48,49] Longer durations of therapy are also under ongoing study in large randomized trials. The Adjuvant Tamoxifen for Longer Against Shorter (ATLAS) Trial is comparing 5 to 10 years, and the Adjuvant Tamoxifen Treatment Offer More (ATTOM) trial is comparing 5 years with various longer durations.

Ovarian Ablation or Suppression in the Premenopausal Setting

The Early Breast Cancer Trialist Cooperative Group analyzed the results of 21 randomized trials that studied ovarian ablation by either surgery or radiation therapy or ovarian suppression in premenopausal women with early breast cancer.[11] This analysis reported that ovarian ablation or suppression alone resulted in a reduction in the annual odds of recurrence and death, an effect that persisted through 15 years of follow-up. The impact of ovarian ablation or suppression in the presence of chemotherapy is less certain (Table 4).

The available clinical trials of ovarian suppression or ablation are subject to substantial limitations. The trials generally did not include tamoxifen as a component of treatment. When tamoxifen was included, it was generally added to the ovarian suppression/ablation arm but not the chemotherapy arm, which makes attributing any advantage to tamoxifen versus ovarian suppression/ablation versus both difficult. Additionally, few trials compared ovarian suppression to anthracycline-containing or taxane-containing regimens commonly used today. Finally, trials were not always limited to patients with ER-positive disease, and many trials were underpowered. Therefore, we may not be able to confidently extrapolate these results to patients with known ER status or treated with anthracycline- or taxane-containing chemotherapy regimens.

The overview reported no significant difference in outcomes comparing chemotherapy alone with chemotherapy plus ovarian suppression or ablation, although the reported benefit was greater in those under age 40 years than in those aged 40 to 49 years. This result suggests that some of the effect of chemotherapy is mediated through toxic effects on ovarian hormone production. For example, most of the women over age 40 will become amenorrheic with current adjuvant chemotherapy. Thus, the effect of chemotherapy may be because of both direct antitumor cytotoxicity and indirect tumor effects from reduction of ovarian hormone synthesis.

Two randomized trials of ovarian suppression or ablation in combination with tamoxifen versus CMF chemotherapy in premenopausal women with ER-positive breast cancer have suggested that ovarian suppression or ablation are at least equivalent to[50] or superior to CMF chemotherapy alone.[51] Neither of these trials incorporated endocrine therapy plus CMF chemotherapy. Thus, whether CMF chemotherapy plus tamoxifen would be equivalent or superior to ovarian suppression or ablation alone cannot be assessed from these trials.

Table 4 Impact of Ovarian Ablation or Suppression Stratified by Age and Presence or Absence of Chemotherapy

	Ratio of Annual Recurrence Rates (SE)		Ratio of Annual Death Rates (SE)	
	< 40 years	40-49 years	< 40 years	40-49 years
Ovarian ablation				
OA vs. nil	30% (17)	33% (8)	29% (16)	32% (9)
OA +chemotherapy vs. chemotherapy alone	4% (11)	10% (8)	-4% (13)	2% (9)
Ovarian suppression				
OS vs. nil	21% (13)	23% (9)	27% (21)	21% (13)
OS + chemotherapy vs. chemotherapy alone	30% (13)	-8% (13)	20% (17)	Negative effect, numbers not stated

Source: Reprinted from Early Breast Cancer Trialists Collaborative Group[11]; with permission.

Randomized studies designed to further explore the role of ovarian ablation and whether triplet therapy (chemotherapy, ovarian suppression, and hormonal therapy) is better than chemotherapy alone or chemotherapy with tamoxifen are ongoing and are designed as outlined below:

SOFT (Suppression of Ovarian Function) Trial: Women who have completed chemotherapy and are still menstruating are randomized to receive: 1) tamoxifen; 2) tamoxifen plus ovarian suppression; or 3) exemestane plus ovarian suppression. The target accrual is 3,000 patients.

TEXT (Tamoxifen and Exemestane) Trial: This trial focuses on women who plan to receive ovarian suppression from the start of adjuvant therapy. These women are randomized to receive ovarian suppression and either concurrent tamoxifen or exemestane. Target accrual is 1,875 patients.

PERCHE (Premenopausal Endocrine Responsive Chemotherapy) Trial: This trial is exploring the role of chemotherapy in women who have undergone ovarian suppression plus either tamoxifen or exemestane. Target accrual is 1,750 patients.

Social Implications of Endocrine Therapy in Young Women

Family planning is an important issue for many younger patients with breast cancer. Although no detrimental impact of pregnancy subsequent to a diagnosis of breast cancer has been found,[52,53] the recommended 5-year duration of tamoxifen therapy may be particularly burdensome to patients who are interested in having children after breast cancer. In this age group, however, the benefit of tamoxifen therapy does not begin to emerge until at least 2 years of therapy and increases up to at least 5-years of tamoxifen therapy.[11] Therefore, limiting tamoxifen therapy to 2 years in premenopausal patients to preserve childbearing options seriously compromises the antitumor benefits of tamoxifen. Although no large-scale studies of ovarian suppression and fertility are available, one study in premenopausal women found that permanent amenorrhea occurred in approximately 59% treated with CMF chemotherapy alone, but that menstrual function resumed in approximately 70% to 80% of patients after treatment with 2 years of goserelin alone.[54] Further study of the duration of ovarian suppression, tamoxifen, and methods of potential ovarian protection are required to address this important issue for young breast cancer survivors.

Aromatase Inhibitors in Premenopausal Women

Aromatase inhibitors (AIs) have not been well studied in premenopausal women with or without ovarian suppression or ablation and thus are only recommended for postmenopausal patients. The use of AIs in young women is associated with the occurrence of benign ovarian pathology. This raises the issue of determining menopausal status at the start of, during, and after therapy. For example, patients may become amenorrheic during adjuvant chemotherapy without permanent loss of ovarian hormone production. Thus, the distinction between a "temporary" versus a permanent menopause must be made. If menopausal status is uncertain after chemotherapy, tamoxifen

should be used as the initial endocrine treatment. Incorrectly assuming that a patient is menopausal and treating with an AI deprives the patient of effective hormonal therapy with tamoxifen.

Aromatase Inhibitors in Postmenopausal Women

Randomized trials using the selective AIs as adjuvant endocrine therapy of postmenopausal women have been reported that have used the selective AIs as either initial therapy versus tamoxifen, sequentially following 2 to 3 years of tamoxifen, or as extended therapy after approximately 5 years of tamoxifen.

Initial Therapy With Aromatase Inhibitor Versus Tamoxifen: The ATAC trial (Arimidex, Tamoxifen Alone or in Combination) recruited 9,366 postmenopausal women with early breast cancer of any estrogen or progesterone receptor status from 1996 to 2000. Results of the trial are now available, with a median follow-up of 68 months.[55] After initial treatment with surgery with or without additional radiation therapy or chemotherapy, patients were randomized to receive tamoxifen versus anastrozole versus tamoxifen plus anastrozole for 5 years. No difference in outcome has been seen between tamoxifen alone and tamoxifen in combination with anastrozole. At 6 years follow up, a 3.3% absolute difference was seen in DFS in patients with hormone receptor–positive disease favoring anastrozole compared with tamoxifen (intent to treat hazard rate = 0.87; 95% CI, 0.78–0.97; P = .01; receptor positive cohort hazard rate = 0.83; 95% CI, 0.73–0.94; P = .005) and recurrence-free survival (intent to treat hazard rate = 0.79; 95% CI, 0.70–0.90; P = .0005; receptor positive cohort hazard rate = 0.74; 95% CI, 0.64–0.87; P = .0002; Figure 4) The reduction in recurrences is related to the prevention of ipsilateral recurrences, new contralateral breast primaries, and distant recurrences. No difference in overall survival has been seen to date.

The BIG 1-98 trial is a 4-arm study that randomized 8,010 postmenopausal women with hormone receptor–positive breast cancer to receive either initial tamoxifen or letrozole or to receive sequential therapy with tamoxifen followed by letrozole or vice versa. Data for the single-drug arms comparing tamoxifen and letrozole combined with the initial treatment period with either tamoxifen or letrozole from the sequential arms have now been presented. With a median follow-up of just over 2 years, DFS favors the use of letrozole compared with

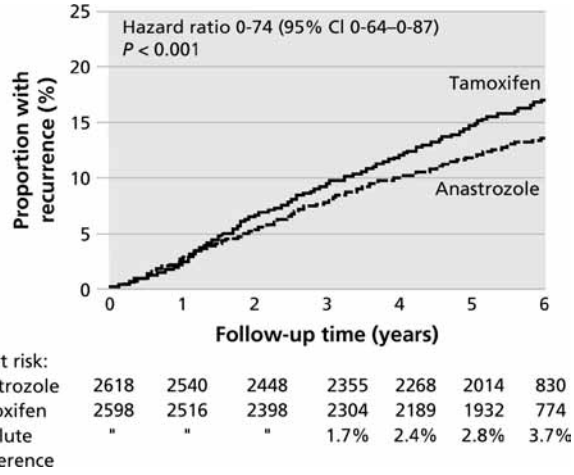


Figure 4 Time-to-recurrence in hormone-receptor—positive patients. Reprinted from Howell et al.[55]; with permission.

tamoxifen (hazard rate = 0.81; 95% CI, 0.70–0.93; P = .003). The impact of sequential treatment in BIG 1-98 has not been reported. The BIG 1-98 trial will provide the first randomized comparison between a 5-year course of an AI and a sequential strategy of tamoxifen followed by an AI or an AI followed by tamoxifen.[56]

Ideally, predictive factors for response to AIs would be identified. Data from the ATAC trial suggested a more dramatic benefit of anastrozole in patients with ER+/PR− tumors compared with ER+/PR+ tumors.[57] However, this finding was not observed in the initial analysis of the BIG 1-98 trial.

Part of Sequential Therapy After 2 or 3 Years of Tamoxifen: In the Intergroup Exemestane Study trial (IES trial), postmenopausal patients with hormone receptor positive breast cancer who had been initially treated with 2 to 3 years of tamoxifen were randomized to continue tamoxifen or to switch to exemestane therapy, both to complete a total of 5 years of endocrine therapy.[58] At a median follow-up time of 30 months after randomization, a 4.7% absolute improvement in 3-year DFS favoring the exemestane group was seen (hazard rate for DFS = 0.68; 95% CI, 0.56–0.82; P = .00005). Exemestane was associated with a decrease in all events affecting DFS (local and distant recurrence, contralateral breast primary, intercurrent death). No significant improvement was seen in overall survival (P = .08).

The Italian Tamoxifen Anastrozole (ITA) Trial randomized 448 postmenopausal women with ER-positive breast cancer who had been treated with 2 to 3 years of tamoxifen to continue tamoxifen or switch

to anastrozole.[59] With 36 months median follow up, DFS was superior with anastrozole (hazard ratio = 0.35; 95% CI, 0.18–0.68; *P* = .001). No difference in survival was documented.

The combined ABCSG 8/ARNO 95 trial randomized postmenopausal women with hormone receptor–positive breast cancer who were treated with tamoxifen for 2 to 3 years and then randomized to continue tamoxifen or switch to anastrozole. At a median follow-up time of 28 months, the anastrozole arm was associated with a 3.1% absolute improvement in 3-year event-free survival (hazard ratio = 0.60; 95% CI, 0.44–0.81; *P* = .0009).[60]

Extended Therapy Beyond 5 Years of Tamoxifen: The MA-17 trial recruited 5,187 postmenopausal women with hormone receptor–positive breast cancer who had received from 4.5 to 6 years of initial adjuvant tamoxifen. Patients were then randomized to receive 5 additional years of extended adjuvant therapy with either letrozole or placebo. The first interim analysis in 2003 reported an estimated 4-year DFS in the letrozole group of 93% compared with 87% in the placebo group.[61,62] Although no significant difference in overall survival was seen, a suggestion of improvement in overall survival was noted with letrozole in patients with node–positive disease (*P* = .05).

None of the studies using the AIs in breast cancer has led to a clear improvement in survival, which is the ultimate goal, and no strategy has shown a clear improvement in quality of life. Additionally, no trials are currently completed that have directly compared initial, sequential, or extended hormonal therapy.

In 2004, ASCO issued a technology assessment on the use of AIs that stated, "Based on results from multiple large randomized trials, adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer should include an aromatase inhibitor. Neither the optimal timing nor duration of aromatase inhibitor therapy is established."[63] This ASCO statement clearly acknowledges the gaps in the data and is fully consistent with the adjuvant endocrine therapy recommendations in the NCCN Breast Cancer Treatment Guidelines.[3]

Patients and physicians must decide on treatment strategies with the AIs and tamoxifen based on studies that are still maturing.

Aromatase inhibitors and tamoxifen have differing side effect profiles. AIs are associated with lower risk of peripheral blood clots and endometrial cancer but a greater risk of bone loss and bone fracture than tamoxifen.

AI treatment can be associated with an arthralgia syndrome of unclear etiology. Both agents are associated with hot flashes, night sweats, and other menopausal symptoms. Quality of life analyses have not shown substantial differences between AIs and tamoxifen; however, patients taking AI therapy tend to report greater sexual dysfunction. Some of the large adjuvant trials have shown an increased incidence of non-breast cancer deaths in patients receiving AIs compared with tamoxifen. For example, in the BIG I-98 trial, total deaths were similar in both study arms, but deaths unrelated to cancer were higher in the letrozole arm (55 of 4,003 vs. 38 of 4,007 patients).[56] In contrast, in the B-14 trial comparing tamoxifen and placebo, a 15% reduction in fatal coronary deaths occurred in the tamoxifen arm. Researchers and clinicans have speculated that if AIs are associated with an increase in cardiac problems, this phenomenon may not be caused by a deleterious effect of the AIs, but to an anti-atherogenic cardioprotective effect of tamoxifen that outweighs its known short-term thrombotic effect. Differences in how data were collected in these studies may further confound the results, but clearly, more data are available regarding long-term effects of tamoxifen than long-term effects of the newer AIs.

Another area of uncertainty is whether early cross-over to or extended therapy with an AI after 5 years of tamoxifen is best. In many cases, this decision will be based on patient preference. Patients taking tamoxifen with few side effects may resist a switch. For patients with health insurance concerns, the issue may be economic, based on the higher financial costs of the AIs, although total costs of 5 years of tamoxifen followed by 5 years of letrozole (10 years total treatment) are higher than 2 to 3 years of tamoxifen followed by an AI to complete 5 years of therapy.

Defining an Optimal Chemotherapy Regimen

Cytotoxic chemotherapy has been known for more than 3 decades to provide benefit in terms of DFS and overall survival in women with invasive breast cancer.[64–67] During this time, a number of chemotherapy regimens have been studied in prospective, randomized clinical trials to try to identify the optimal chemotherapy regimen.

To date, no single optimal chemotherapy regimen has been identified. However, a number of considerations do distinguish the various chemotherapy regimens.

Role of Anthracyclines

The anthracyclines are among the most active agents in the treatment of breast cancer. The role of the anthracyclines as adjuvant therapy, specifically selection criteria for patients who should preferentially benefit from anthracyclines versus those who are unlikely to benefit, continues to be uncertain.

In 1998, the Early Breast Cancer Trialists' Collaborative Group published an overview analysis of anthracyclines in early breast cancer,[68] which was further updated in 2005.[11] The updated analysis included data from some 14,000 patients participating in studies comparing anthracycline-based chemotherapy to CMF. The analysis documented a modest benefit favoring the anthracycline-based regimens in DFS (recurrence rate ratio, 0.89; SE, 0.03; $P = .001$) and breast cancer death rate ratio (0.84; SE, 0.03; $P < .00001$).[11] The beneficial impact of anthracycline regimens is seen across all age groups, including younger than 50 and older than 70 (although relatively few patients > 70 have participated in clinical trials). Other studies have shown that anthracycline regimens combined with CMF are associated with improved results.[69]

The number of cycles of anthracycline-based chemotherapy used is an important treatment variable. In the overview analysis,[11] if the 4 trials that included 4 or fewer cycles of epirubicin or doxorubicin are omitted, the beneficial effect of an anthracycline-based regimen increased to 31%. Specifically, 6 to 9 cycles of an anthracycline regimen results in an approximate 25% decrease in mortality over a CMF regimen. Multiple different generations of anthracycline regimens have been used, with a general pattern of prolonging and increasing the dosages of chemotherapy, resulting in an incremental improvement in outcomes. For example, as seen in Figure 5, the original regimen of FEC 50 has segued to FEC 1 or CEF, and AC therapy has evolved to dose-dense AC therapy followed by paclitaxel.

Therefore, the overall data suggest a benefit with anthracycline either in lieu of or added to CMF. However, not all anthracycline regimens confer the same advantage. For example, the MA-5 trial (CEF vs. CMF) showed an improvement in DFS favoring the anthracycline regimen, but the B-15 trial (AC vs. CMF) and the FASG trial (FEC 50 vs. CMF) demonstrated equivalent outcomes.[70] This particular observation may be due to the greater incidence of amenorrhea with CEF in MA-5 and the lack of use of adjuvant endocrine treatment in the trial.

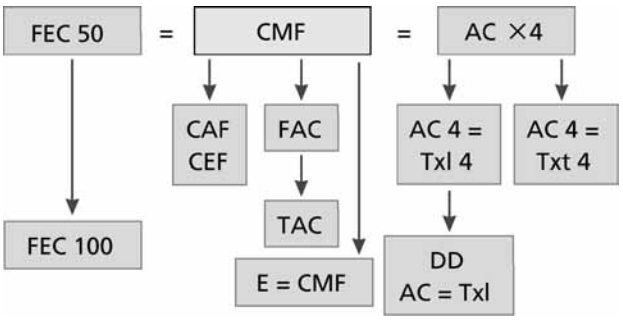


Figure 5 Reframed thinking on adjuvant therapy: the generation lineages and chains of interference.

Numerous studies have suggested an interaction between anthracyclines and HER2/*neu* status. Retrospective analysis of randomized trials suggests that patients with HER2-positive tumors benefit more from the use of an anthracycline-containing regimen compared with a non-anthracycline–containing regimen, while patients with HER2-negative tumors may show no increase in benefit.[71–73] The explanation for this interaction is uncertain, but one hypothesis is that HER2 expression is a surrogate for topoisomerase-II-alpha expression, which may in turn predict doxorubicin sensitivity.

Recent results showing trastuzumab as an effective adjuvant therapy for patients with tumors over-expressing HER2 provide some concern regarding the use of anthracycline-containing regimens.[74,75] Both trastuzumab and the anthracyclines have cardiac toxicity, and the combination in the metastatic setting appears to have worse cardiac toxicity than either treatment alone.[76] The incorporation of trastuzumab into the adjuvant chemotherapy regimen in patients with tumors overexpressing HER2 appears important, although uncertainty remains about the role of the anthracyclines in the presence of trastuzumab. Issues include whether the early reduction in recurrence with trastuzumab will persist with longer follow-up times and whether adding an anthracycline will better prevent late occurrences. Some of these questions may be answered from the results of the BCIRG 006 study, which includes a non-anthracycline–containing adjuvant chemotherapy plus trastuzumab arm. Additionally, whether anthracycline-based regimens can be avoided for patients with HER2-negative tumors requires further study and consideration.

Although the toxicities of epirubicin and doxorubicin are similar, higher doses of epirubicin are generally better tolerated than doxorubicin. Cardiac toxicity is a recognized complication of the anthracyclines; doxorubicin has a higher risk than epirubicin on a milligram per milligram basis. At apparently equally efficacious doses, when corrected for potency, the risk of cardiac toxicity appears similar for doxorubicin and epirubicin.

The rate of cardiac toxicity increases if patients receive chemoradiotherapy with a radiation therapy field that includes the heart. Data from the 1970s suggested that risk of cardiac toxicity rises sharply to 5% at a cumulative dose level of 550 mg/m^2.[77] The risk of doxorubicin-associated cardiac toxicity was further studied in more contemporary trials as part of the research surrounding dexrazoxane, a cardioprotective agent.[78] In this dataset, the risk of cardiac toxicity rose sharply to over 20% at a cumulative dose of 550 mg/m^2. Based on this analysis, doxorubicin cardiac toxicity may become a concern at a cumulative dose as low as 400 mg/m^2. The incidence of secondary leukemias with anthracycline-based chemotherapy is higher than with CMF regimens (1.3%–1.7% with AC or CEF vs. 0.4% with CMF).[79]

Role of the Taxanes

Five large, adequately powered trials of adjuvant taxanes have been reported. Four of these trials enrolled women with axillary lymph node–positive breast cancer, and a fifth enrolled women in the neoadjuvant setting. Different chemotherapy regimens were used, including those that gave the taxane concurrently versus sequentially after an anthracycline. Additionally, the trials variably reported results according to ER status, HER2/*neu* status, age, or lymph node involvement.

CALGB 9344/Intergroup 0148: A total of 3,121 patients with axillary lymph node–positive breast cancer were randomized to receive 1 of 3 dose levels of doxorubicin (60 mg/m^2, 75 mg/m^2, or 90 mg/m^2) in combination with cyclophosphamide (600 mg/m^2) with or without sequential paclitaxel. No differences in efficacy were seen based on the dose of doxorubicin. The addition of paclitaxel was associated with an improvement in both DFS (hazard ratio = 0.83; 95% CI, 0.73-0.94; adjusted P = .0023) and overall survival (hazard ratio = 0.82; 95% CI, 0.71–0.95; adjusted P = .0064) in patients with early stage lymph node–positive breast cancer.[80] Assessment of efficacy by ER status documented that the subgroup of patients with ER-negative disease experienced a DFS advantage with the addition of paclitaxel extending for 10 years, but no statistically significant long-term benefit for paclitaxel was seen in patients with ER-positive disease (Berry et al., unpublished data).

NSABP B-28: This study of 3,060 women with axillary lymph node–positive breast cancer investigated AC chemotherapy with or without sequential paclitaxel. An improvement with the addition of paclitaxel was seen in DFS (relative risk for recurrence, 0.83; 95% CI, 0.72–0.95; P = .006) but not overall survival (relative risk for death, 0.93; 95% CI, 0.78-1.12; P = .46.[81] In contrast to the results of CALGB 9344, no interaction was seen between ER status and DFS.

BCIRG 001: This study randomized 1,491 women with axillary lymph node–positive breast cancer to receive 6 cycles of TAC (paclitaxel, doxorubicin, cyclophosphamide) versus 6 cycles of FAC (5-fluorouracil, doxorubicin, cyclophosphamide). TAC was associated with both an improved relapse-free (hazard ratio, 0.72; 95% CI, 0.59–0.88; P = .001) and overall survival (hazard ratio, 0.70; 95% CI, 0.53–0.91; P = .008) in both ER-positive and ER-negative tumors.[82] The superiority of TAC over FAC appeared independent of number of involved lymph nodes, hormone-receptor status, HER2/*neu* status, and menopausal status.

The PACS-01: This trial compared 6 cycles of FEC (5-FU, epirubicin, cyclophosphamide) and 3 cycles of FEC followed by 3 cycles of docetaxel in 1,999 women with node–positive breast cancer.[83] DFS was superior with the addition of docetaxel (hazard rate, 0.83; 95% CI, 0.69–0.99; P = .041) as was overall survival (hazard rate, 0.77; 95% CI, 0.59–1.00; P = .05). Analysis by age showed a DFS advantage with the addition of docetaxel in patients 50 years of age and older, but not those younger than 50 years of age. This result is somewhat surprising, because adjuvant chemotherapy has generally tended to show a greater benefit for younger patients.

NSABP B-27 3-Arm Trial: This trial studied the benefit of 4 cycles of neoadjuvant AC chemotherapy alone, followed sequentially with neoadjuvant docetaxel, or followed sequentially with postoperative docetaxel in a total of 2,411 women with operable breast cancer.[84] DFS and overall survival were not significantly different among the 3 treatment groups.

These trials are difficult to compare because of different definitions of outcomes, differing methods for assessing hormone receptor status, differing doses and schedules, and differing taxane used. Therefore, definitively identifying subgroups of patients who would benefit from specific taxane-containing regimens is not possible. Ongoing trials address this issue. ECOG 1199, comparing AC followed by weekly or every-3-week paclitaxel or docetaxel, showed no significant difference between the taxanes or taxane schedule in disease-free or overall survival.[85] Weekly docetaxel was the most difficult drug to administer at planned dose levels. NSABP B-38 is comparing TAC versus dose-dense AC then dose-dense paclitaxel versus dose-dense AC followed by dose-dense paclitaxel plus gemcitabine.

Trastuzumab in the Adjuvant Setting

Findings from several trials testing the addition of trastuzumab in the adjuvant therapy of HER2/*neu* overexpressed breast cancer were presented in 2005.

NCCTG N9831 and NSABP B-31: These trials randomized patients with HER2/*neu* overexpressed invasive breast cancer to receive doxorubicin and cyclophosphamide (AC) followed by paclitaxel with or without additional trastuzumab.[75] Both trials also permitted the use of tamoxifen, and in 2003 also permitted the use of AIs for postmenopausal women. NSABP B-31 was limited to women with axillary lymph node–positive breast cancer. N9831 was initially restricted to women with node–positive breast cancer, but was amended in 2003 to include high-risk node–negative disease (tumors larger than 1 cm if ER-negative or larger than 2 cm if ER-positive). Patients with current or prior cardiac disease were excluded.

NSABP B-31 used trastuzumab begun concurrently with paclitaxel. The N9831 trial included an arm with trastuzumab begun concurrently with paclitaxel and an arm of sequential trastuzumab begun after paclitaxel. This makes N9831 trial the only trial to directly compare concurrent versus sequential trastuzumab.[86] Analysis of the N9831 trial included a pair-wise comparison of the sequential and the concurrent arms compared with control and an additional comparison of the sequential versus the concurrent arms. The two control arms and the concurrent trastuzumab arms of the B-31 and N9831 were combined for a joint analysis.[87,88]

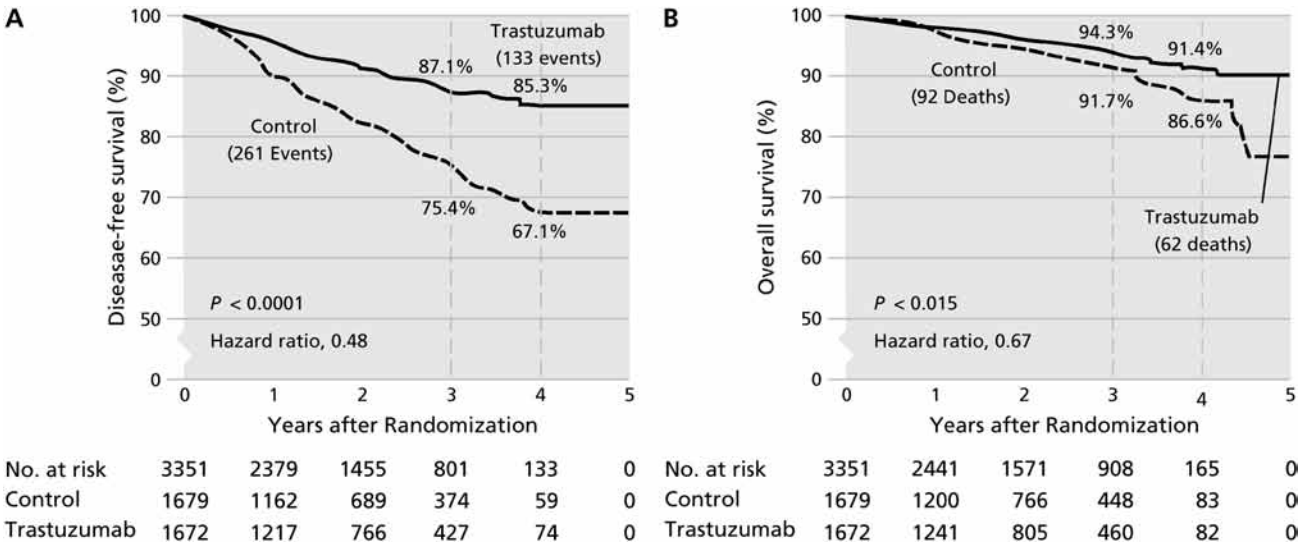
The joint analysis included 3,351 patients: 1,736 from B-31 and 1,615 from N9831. The 4 groups (control and experimental arms from each protocol) were well balanced with respect to age, nodal involvement, ER and PR status, and tumor size. Median follow up for the pooled analysis was 2.0 years, with medians of 2.4 years for B-31 and 1.5 years for N9831. The primary endpoint was DFS. Secondary endpoints included overall survival, freedom from first distant recurrence, and cardiac toxicity. The combined analysis included 395 events, which prompted the first interim analysis.

In the pooled analysis with 2 years of median follow-up, trastuzumab given concurrently with paclitaxel after AC chemotherapy was shown to improve DFS (hazard ratio = 0.48; 95% CI, 0.39–0.59; < .0001; Figure 6). The DFS benefit was of similar magnitude in patients stratified based on nodal status, tumor size, hormone receptor status, age, tumor grade, and histologic type of breast cancer, and was statistically significant except in the axillary lymph node–negative subset and in those with favorable histologic grade in whom the number of events was small. Overall survival was also superior with trastuzumab (hazard ratio = 0.67; 95% CI, 0.48–0.93; *P* = .015; Figure 6).

The N9831 trial showed a 36% reduction in recurrence in patients receiving concurrent trastuzumab compared with sequential trastuzumab.[89] The N9831 trial showed a 13% reduction in recurrence for the group receiving sequential trastuzumab compared with the control group (not receiving trastuzumab). This difference was not statistically significant. The HERA trial also used sequential administration of trastuzumab, with somewhat different results than those seen in the sequential arm of N9831.

BIG 01-01 (HERA Trial): The HERA trial enrolled women with breast cancers overexpressing HER2/*neu* with positive axillary nodes or high-risk node–negative disease (tumors > 1 cm). Patients were randomized to receive either no adjuvant trastuzumab or 1 or 2 years of sequential trastuzumab after completing local therapy and an approved adjuvant chemotherapy regimen. Prior adjuvant or neoadjuvant chemotherapy was administered to all patients, although the type was at the investigators' discretion. Subjects had to complete primary management with surgery, adjuvant chemotherapy, and/or radiation therapy before enrollment.

A planned intent-to-treat interim analysis of 1 year of trastuzumab compared with control has been



No. at risk	3351	2379	1455	801	133	0
Control	1679	1162	689	374	59	0
Trastuzumab	1672	1217	766	427	74	0

No. at risk	3351	2441	1571	908	165	0
Control	1679	1200	766	448	83	0
Trastuzumab	1672	1241	805	460	82	0

Figure 6 Kaplan-Meier estimates of disease-free survival (A) and overall survival (B). The hazard ratios are for the comparison of the trastuzumab group with the control group.

Source: Reprinted with permission from Romond et al.[75]

reported.[75] The 2 arms in the interim analysis were well balanced for age, adjuvant chemotherapy regimen, menopausal status, nodal status, hormone receptor status, and adjuvant endocrine therapy. Patients were stratified by nodal status, adjuvant chemotherapy regimen, hormone receptor status, endocrine therapy, age, and geographic region. The results showed that trastuzumab every 3 weeks for 1 year after adjuvant chemotherapy significantly prolonged DFS (hazard ratio = 0.54; 95% CI, 0.43–0.67; $P < .0001$). Trastuzumab also decreased the risk of distant metastases (hazard ratio = 0.49; 95% CI, 0.38–0.63; $P < .0001$). Trastuzumab benefits were shown to be independent of baseline characteristics such as nodal status and type of adjuvant chemotherapy. Survival was not statistically significantly different (hazard ratio = 0.76; 95% CI, 0.47–1.23; $P = .26$). Results regarding optimal duration of trastuzumab (1 vs. 2 years) should be available in 2008.

Together, the NSABP B-31, N9831, and HERA trials consistently show a large and statistically significant improvement in DFS for early-stage HER2-positive breast cancer. Results of a fourth trial, BCIRG 006, are expected shortly.

In addition, a study by Buzdar et al.[89] randomized patients to receive neoadjuvant chemotherapy with either 4 cycles of paclitaxel followed by 4 cycles of FEC or the same chemotherapy with simultaneous weekly trastuzumab. It was stopped early because trastuzumab plus chemotherapy showed superiority in pathologic complete response rates (66.7% vs. 25%; $P = .02$). This regimen will be tested further in a future NSABP clinical trial.

Sequential Versus Concurrent Therapy: Whether trastuzumab should be optimally administered sequentially or concurrently with adjuvant chemotherapy is still uncertain. HERA reported a substantial and statistically significant benefit for sequential therapy compared with no trastuzumab. In contrast, N9831 reported no difference in DFS between the sequential trastuzumab and control arms, with a significant improvement in the concurrent trastuzumab arm compared with sequential trastuzumab. Follow-up times are relatively short on all of these trials, and further follow up is required before definitive conclusions can be reached.

Determination of HER2/neu Status: HER-2/*neu* status can be assessed either using immunohistochemistry (IHC) or fluorescent in situ hybridization (FISH) techniques. When concordance between local and central laboratories for HER2/*neu* testing by IHC and FISH was analyzed, only a modest level of concordance was seen.[86] This shows that the laboratory techniques used to determine the level of amplification or expression of HER2/*neu* are an important variable in determining candidacy for trastuzumab. Current guidelines recommend testing for HER2/*neu* level of expression using either IHC or FISH, using FISH analysis to confirm intermediate IHC results. Further clarification of the prognostic

and predictive value, diagnostic accuracy, and cost-benefit of IHC versus FISH testing is the subject of ongoing investigation.

Cardiac Toxicity: Congestive heart failure is associated with trastuzumab, particularly in patients also receiving an anthracycline.[77] For example, the B-31 trial showed a 4% incidence of congestive heart failure in the treatment group compared with 0.03% in the control group. An additional 15% of B-31 patients receiving trastuzumab stopped therapy for asymptomatic decreases in left ventricular ejection fraction. In the N9831 trial, the rate of cardiac events was 0% in the control arm, 2.2% in the sequential arm, and 3.3% in the concurrent arm. The sequential 1-year arm of trastuzuab of the HERA trial showed a 0.5% rate of clinical cardiac events; however, results were reported after only 1 year median follow-up compared with 1.5 years in N9831 and 2.4 years in NSABP B-38. Both of these studies showed a higher rate of cardiac events.

Most patients with trastuzumab cardiac toxicity appear to experience cardiac improvement when trastuzumab is discontinued. However, long-term cardiac effects are unknown. Additionally, the trials either excluded patients or prohibited additional trastuzumab in patients with poor cardiac function after initial chemotherapy or while receiving trastuzumab. Cardiac monitoring is important to avoid the potential for a higher rate of clinical cardiac events. Further information regarding risk factors, natural history, and impact of interventions relating to trastuzumab cardiac toxicity are needed.

Role of Trastuzumab in Patients Undergoing or Recently Completing Adjuvant Chemotherapy: The results of the trastuzumab adjuvant trials raise questions about offering trastuzumab to patients currently receiving adjuvant chemotherapy or who have recently completed adjuvant chemotherapy. For example, in the N9831 trial, participants in the sequential arm currently receiving initial AC were offered trastuzumab as part of the study. Patients randomized to the control arm were also offered trastuzumab if they are within 6 months of completing the adjuvant therapy. However, this 6- (or 12-) month recommendation is based on expert consensus rather than prospective data. These initial data may prompt physicians to offer trastuzumab to patients with HER2-overexpressing breast cancer who have completed recent adjuvant therapy. However, this group of patients will diminish in size as adjuvant therapy with trastuzumab is integrated into practice.

Chemotherapy in the Older Patient

Age is a prognostic and predictive factor for adjuvant chemotherapy in breast cancer. In part this is because adjuvant therapy may benefit older patients less because of competing non-breast cancer morbidities and mortality.

The risk of breast cancer death as a function of stage and age is remarkably consistent across ages over 40 years (Figure 7).[90] In contrast, considerable differences in non breast cancer mortality begin at age 60 to 65 years. Specifically, a woman who is 70 years when early breast cancer is diagnosed is 2 or 3 times more likely to die of non-breast cancer causes than of breast cancer. For example, *Adjuvant! Online* estimates that a 68-year-old women in average health with a 2.8-cm, grade 2 tumor, node negative and ER-positive tumor, has a 10-year risk of morality from breast cancer of 15.2% when treated with local therapy alone and non-breast cancer related 10-year mortality risk of 19.9%. With the addition of a third-generation chemotherapy regimen plus an AI, the 10-year mortality from breast cancer is 7.5% compared with non-breast cancer mortality of 19.9%. For older women, competing causes of mortality rapidly increase with increasing age.

Table 5 depicts the annual death rates with polychemotherapy and tamoxifen use in patients according to age who have ER-positive breast cancer. The numbers in each column represent the ratio of death for treatment versus no treatment. Although the benefits from tamoxifen are not age-dependent, the

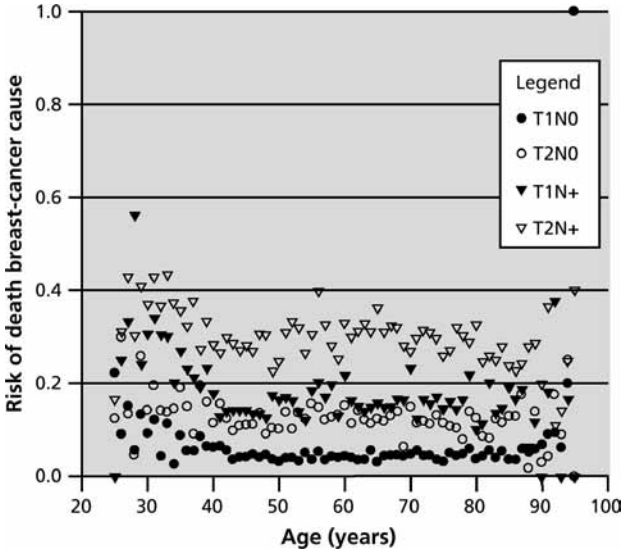


Figure 7 Risk of breast cancer death as a function of stage and age.
Source: Reprinted with permission from Vinh-Hung et al.[90]

Table 5 Effect of Therapy Versus No Treatment in Breast Cancer

	Ratio of Annual Death Rates Treatment:Control	
Age	**Chemotherapy**	**Tamoxifen**
<40	0.71	0.61
40-49	0.70	0.76
50-59	0.85	0.76
60-69	0.91	0.65
70+	0.87	0.63

benefits from chemotherapy are substantially related to age, with the most dramatic improvement associated with chemotherapy occurring in women under the age of 40 years.

When these data are translated into absolute risks/gains with chemotherapy at 15 years follow up, a 12.3% absolute improvement in breast cancer recurrence is seen for patients younger than age 50, with only a 4.1% improvement seen for those ages 50 to 69. Similarly, a 10% improvement in breast cancer mortality is seen in the younger group compared with only 3% in the older group. If data are subdivided according to ER status, a 4.9% benefit in recurrence risk is seen for older women with ER-positive tumors compared with 7.6% for younger women. However, 73% of older women with ER-positive tumors are also node positive, compared with only 34% of younger women. One might expect a greater benefit in patients with node–positive disease, but this is not true for women 50 to 69 years. Limited data from women over 69 years are available, but the improvements are likely to be even smaller for this age subset. The Early Breast Cancer Trialists' overview also examined non-breast cancer mortality in the first year after diagnosis, in large part reflecting treatment-related mortality. This analysis provided the sobering suggestion that women over age 60 who received chemotherapy had greater mortality in the first two years than those who did not, although the differences were not statistically significant.[11]

Several randomized studies have reported results for node–positive and -negative disease as a function of age. A combined analysis of the NSABP B-20 and B-14 trials examined the effect of age on recurrence-free survival in women with ER-positive, node–negative disease treated with placebo, tamoxifen, or tamoxifen combined with CMF.[37] The risk of recurrence in the placebo groups was highest in those younger than 50 years. After 50 years of age, the curves were similar in all age groups studied (< 49, 50-59, and > 60 years). In the older age group, tamoxifen had a more potent therapeutic effect, and the incremental gains associated with chemotherapy were more modest.

The level of estrogen receptor expression increases with age and may be responsible for the differential impact of endocrine therapies with age. Specifically, median quantitative concentrations of ER are 2 or 3 times greater in patients age 60 years or older than in patients younger than 50 years. The combined analysis of the B-14 and B-20 trials divided patients into those with low ER level tumors (0-49 fmol/mg) and high ER level tumors (e 50 fmol/mg). The results of B-20 suggest that although the addition of CMF benefits both groups, patients with low levels of ER expression benefit more than those with higher levels of ER expression. In contrast, the benefit of tamoxifen in B-14 was greater in those with high levels of ER. Data analyzed using menopausal status also suggest that the benefit of chemotherapy added to tamoxifen in terms of recurrence-free survival is smaller than the benefit of added tamoxifen alone in postmenopausal women.

The IBCSG VII trial was a trial in postmenopausal women with axillary lymph node–positive breast cancer that compared tamoxifen alone versus tamoxifen plus CMF chemotherapy given early versus delayed versus both early and delayed.[91] The addition of CMF provided an approximate 20% decrease in the risk of a disease event (P = .05). IBCSG IX was a trial in postmenopausal women with axillary lymph node–negative breast cancer that randomized patients to receive tamoxifen alone versus CMF for 3 cycles followed by tamoxifen. No difference in DFS was seen. A combined analysis of IBCSG VII and IBCSG IX suggests that lower levels of ER are associated with greater benefit from adding chemotherapy to tamoxifen.

The Breast Intergroup Trial 0100 enrolled patients with node–positive disease who were randomized to receive tamoxifen alone or tamoxifen either concurrent or subsequent to CAF chemotherapy. Among patients with high levels of ER receptors, no benefit in DFS was associated with CAF combined with tamoxifen compared with tamoxifen alone, although a benefit in DFS was seen in those with low levels of ER expression.[38]

In 2005, Muss et al.[32] reported a combined analysis of 4 randomized trials in patients with node–positive breast cancer conducted between 1975 and 1999. This

analysis compared the benefits and toxicities of adjuvant therapy in women in age groups of 50 years or younger, 51 to 64, and 65 years or older. The age distribution in these trials reflects the low rates of accrual of older women to clinical trials; of 6,487 women, 8% were 65 years or older and only 2% were 70 years or older. The older women tended to have higher-risk tumors. For example, more women over the age of 65 had more than 3 positive nodes compared with younger patients; 25% of those over 65 had 10 or more positive nodes compared with 11% of younger women. These demographics reflect the bias of enrolling patients with high-risk disease into clinical trials. Death because of treatment in the first year was 0.2% in those 50 years old and younger, 0.7% in those 51 to 64, and 1.5% in those 65 or older, raising concern regarding the tolerability of chemotherapy in the older women. Chemotherapy regimens were broadly divided into "more chemotherapy" versus "less chemotherapy," and data were also stratified by age group. The analysis suggested that regardless of age more chemotherapy showed a benefit in both DFS and overall survival compared with less chemotherapy. Although these results seem to contradict those presented in the previous discussion, these data reflect the high-risk status of the older women and also reflect selection bias for healthier women in the older age category.

Sequencing Chemotherapy with Radiation Therapy

The optimal integration of chemotherapy with radiation therapy for patients with early-stage breast cancer undergoing breast-conserving surgery has been studied in a variety of clinical trials. One trial assessing the sequence of chemotherapy and radiation therapy was conducted from 1984 to 1992 and randomized 244 patients to receive adjuvant chemotherapy either before or after radiation therapy.[92] Patients predominantly had node–positive disease, but about 20% had high-risk node–negative disease, defined as ER-negative tumors or tumors with lymphovascular invasion. With a median follow up of 135 months, no significant differences were observed between the treatment groups in local recurrence, nodal recurrence, distant recurrence, or overall survival. However, a statistically significant interaction of margin width with risk of local recurrence occurred. Patients with "close" microscopic resection margins (≤ 1 mm) who received radiation therapy first had a 4% local recurrence rate, compared with 32% for patients who received chemotherapy first. In contrast, no significant difference was seen in recurrence rate among those with more widely uninvolved margins (13% with radiotherapy first and 6% with chemotherapy first). No difference was seen in distant failure rates for the entire population, whether radiation or chemotherapy was given first. However, in the subgroup of patients with 4 or more positive nodes, a trend was seen toward a decreased distant failure rate in those receiving chemotherapy first (31% vs. 47%).

An additional study analyzed the impact of surgical margins on local recurrence rates.[93] Outcomes were assessed for patients with node–positive breast cancer treated with immediate or delayed radiation therapy in addition to chemotherapy at a median follow-up of 69 months. Among 37 patients with unknown, positive, or close margins, the local failure rate was 5% in those treated with radiation therapy within 120 days of surgery versus 24% for those with radiation initiated beyond 120 days. No difference was seen in local failure rates in 48 patients with negative margins (defined as greater than 2 mm) between these groups (0% and 5%, respectively).

One approach that might reduce the risk of local failure without interfering with the initiation of chemotherapy is to begin radiation therapy and chemotherapy more or less simultaneously. In a randomized trial in France from 1996 to 2000, 706 patients who had undergone breast-conserving surgery were randomized to receive either concurrent chemotherapy with 5-fluorouracil, mitoxantrone, cyclophosphamide (FNC) and radiation therapy or 6 cycles of FNC followed by radiation therapy.[94] With a median follow-up of 37 months, local-regional failure rates were nearly the same for the early and late radiotherapy arms (3.5% and 4.3%, respectively) with no difference in DFS. Patients with positive axillary nodes in the early radiotherapy arm had a lower local-regional failure rate than those with delayed radiation therapy (3.8% vs. 7.5%), although the difference was not statistically significant. However, the trial results were not reported according to margin widths, which were wider than 1 mm in 86% of patients. Thus, they may not be relevant to the patients at highest risk of local failure if radiation therapy is delayed.

In a pilot study conducted in Boston giving concurrent radiation therapy and CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) with a minimum potential follow-up of 63 months, the risk

of local recurrence was the same for patients with margins wider than 1 mm (6%), close margins (6%), and positive margins (8%).[95] However, concurrent chemotherapy-radiotherapy programs generally have higher acute and long-term toxicity rates than sequential programs, especially when anthracyclines or taxanes are used.

Few data are available on how best to integrate chemotherapy and postmastectomy radiation therapy. A recent analysis of CALGB 9344 data found crude local-regional failure rates of 4% for 98 patients irradiated after 4 cycles of cyclophosphamide-doxorubicin (given every 3 weeks) and 5% for 87 patients irradiated after 4 cycles of the regimen followed by 4 cycles of paclitaxel (also given every 3 weeks).[96]

Summary

The decision making processes surrounding the use of adjuvant endocrine therapy, chemotherapy, and biologic therapy in the treatment of invasive breast cancer are complex. Estimates of the individual woman's likelihood of recurrence or death from breast cancer may be made based on anatomic staging of disease in conjunction with tumor histology, ER and PR status of the tumor, level of HER2/*neu* expression, age of the patient, and co-morbidity. New methods of further refining prognosis, based on DNA microarrays and gene expression, offer the potential for making more reliable and accurate estimates.

A number of factors predict for responsiveness to endocrine therapy, chemotherapy, and trastuzumab in the adjuvant setting. The presence of ER and PR strongly predicts for benefit from the application of endocrine therapy with tamoxifen in all menopausal subsets, from ovarian ablation or suppression in premenopausal women, and from inclusion of AIs in the treatment of postmenopausal women. Whether adjuvant ovarian ablation adds benefit in premenopausal women treated with tamoxifen or improves outcome in combination with contemporary cytotoxic combination chemotherapy remains unknown. No clearly superior strategy for incorporating AIs in the adjuvant therapy of postmenopausal women is yet identified.

Benefit from the application of a variety of cytotoxic chemotherapies may be predicted by younger age and lower levels of estrogen receptor, and possibly by level of expression or amplification of HER2/*neu* and gene microarray and RT-PCR signatures. To date, no best chemotherapy regimen can yet be defined for individual women.

The application of trastuzumab in the adjuvant setting in women with HER2/*neu* amplified or overexpressed breast cancer substantially improves disease free survival and probably overall survival. The optimal duration, schedule, or sequence of trastuzumab in the adjuvant setting is not yet known.

Substantial advances have been made in the adjuvant systemic treatment of women with invasive breast cancer. Decision-making regarding adjuvant therapy for the individual woman remains a complex collaborative process between patient and physicians, balancing risks, benefits, patient preference, and overall goals of treatment.

In summary:

- Well established and reliable prognostic factors in women with local-regional breast cancer include tumor size, axillary lymph node status, tumor histology and grade.
- Gene expression as assessed by gene microarray techniques or reverse transcriptase-PCR may help refine prognostic and predictive information beyond conventional factors such as tumor size, nodal status, and ER and PR levels.
- Computer-based models are available that allow the reliable estimation of prognosis and benefits from systemic adjuvant therapy based on classic anatomic and histologic factors.
- Women of all age groups with ER-positive breast cancer benefit from the use of adjuvant tamoxifen, and the benefits are largely independent of age.
- The benefits of adjuvant cytotoxic chemotherapy decrease with increasing age.
- The benefits of adjuvant cytotoxic chemotherapy decrease with increasing intra-tumoral ER level.
- The decreasing benefit of cytotoxic chemotherapy with increasing age may be related to the higher intra-tumor ER-levels found with increasing age at diagnosis. Older women with ER-poor breast cancers may benefit from the application of cytotoxic chemotherapy
- Ovarian ablation or suppression is at least equivalent to CMF chemotherapy in premenopausal women with hormone receptor-positive breast cancer.
- The value of ovarian ablation or suppression in combination with chemotherapy in premenopausal women remains uncertain.

- Women over the age of 70 years are greatly underrepresented in clinical trials of breast cancer.
- Adjuvant endocrine therapy incorporating an AI in postmenopausal women with ER-positive breast cancer appears superior to tamoxifen alone. The available evidence is not yet sufficient to support the superiority of any one of the selective aromatase inhibitors or any one strategy that incorporates an aromatase inhibitor.
- Adjuvant chemotherapy regimens incorporating an anthracycline appear overall superior to those regimens not containing an anthracycline. The benefits of an anthracycline containing regimen are especially apparent against tumors that overexpress HER2/*neu*.
- Adjuvant chemotherapy regimens that incorporate a taxane have inconsistent benefits in DFS and overall survival.
- First-generation adjuvant trastuzumab studies have shown a consistent and substantial advantage in DFS and the suggestion of improved overall survival.
- The role of cytotoxic chemotherapy in the treatment of older women with breast cancer remains uncertain.

Generally, adjuvant chemotherapy should be administered before breast or chest wall radiation therapy, although patients with a close tumor-free margin may have higher rates of local recurrence with a delay in the start of radiation therapy.

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Post-test Please circle the correct answer on the enclosed answer sheet.

1. Benefit from the application of a variety of cytotoxic chemotherapies may be predicted by younger age and lower levels of estrogen receptor, and possibly by level of expression or amplification of HER2/*neu*.
   True
   False
2. In the current NCCN Breast cancer guidelines, tumor histology is one of the stratification factors.
   True
   False
3. Gene expression using either gene microarray techniques or reverse transcriptase-polymerase chain reaction (PCR) can not provide more precise or reproducible prognostic information than conventional factors.
   True
   False
4. Although predictive factors exist for response to chemotherapy, clinicians currently lack predictive factors for response to endocrine or trastuzumab therapy.
   True
   False
5. In premenopausal women, the benefit of tamoxifen therapy begins to emerge after 1 year. Therefore, limiting tamoxifen therapy to 2 years in these patients to preserve childbearing options does not compromise tamoxifen's antitumor benefits.
   True
   False
6. HER-2/neu status can be assessed either using immunohistochemistry (IHC) or fluorescent in situ hybridization (FISH) techniques.
   True
   False
7. In the ATAC trial, after 6 years of follow up, disease-free survival rates for postmenopausal patients with hormone-receptor positive disease were improved for those taking anastrazole compared with tamoxifen after initial treatment.
   True
   False
8. Analysis of randomized trials suggests that patients with HER2-positive tumors benefit more from an anthracycline-containing regimen than a non-antracycline—containing regimen while patients with HER2-negative tumors may show no increase in benefit.
   True
   False
9. The results of the HERA clinical trial showed that trastuzumab every 3 weeks for 1 year after adjuvant chemotherapy significantly prolonged disease-free and recurrence-free survival rates in HER2+ early breast cancer.
   True
   False
10. The N9831 trial showed a 36% reduction in recurrence in breast cancer patients receiving doxorubicin and cyclophosphamide (AC) concurrent with trastuzumab compared with sequential trastuzumab.
    True
    False

Post-Test Answer Sheet

Please circle one answer per question. A score of at least 70% on the post-test is required.

1.	T	F
2.	T	F
3.	T	F
4.	T	F
5.	T	F
6.	T	F
7.	T	F
8.	T	F
9.	T	F
10.	T	F

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NCCN Task Force Report: Adjuvant Therapy for Breast Cancer

Release Date: March 8, 2006
Expiration Date: March 8, 2007

Please evaluate the achievement of the learning objectives using a scale of 1 to 5. (1=not met; 3=partially met; 5=completely met)	Please indicate the extent to which you agree or disagree with the following statements: (1=Strongly disagree; 3=Not sure; 5=Strongly agree)
Explain how biologic markers such as HER2 status, quantitative estrogen receptor, or genetic markers can be incorporated as prognostic or predictive factors. 1 2 3 4 5	The material was presented in a fair and balanced manner. 1 2 3 4 5
Explain the limitations and strengths of existing risk assessment tools. 1 2 3 4 5	The information presented in this monograph was pertinent to my educational needs. 1 2 3 4 5
Discuss the use of cytotoxic chemotherapy based on risk assessment. 1 2 3 4 5	The information presented was scientifically rigorous and up-to-date. 1 2 3 4 5
Identify the role of tamoxifen therapy in younger women. 1 2 3 4 5	The information presented in this monograph has motivated me to modify my practice. 1 2 3 4 5
Describe the role of aromatase inhibitors and the data supporting their use in postmenopausal women. 1 2 3 4 5	I would recommend this monograph to my colleagues. 1 2 3 4 5
Summarize the role of trastuzumab in the adjuvant setting. 1 2 3 4 5	

Comments and suggestions:_____

_____

_____

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I certify that I have participated in this activity as designed.

Signature_____ Date_____

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