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# Factors Predictive of Distant Metastases in Patients With Breast Cancer Who Have a Pathologic Complete Response After Neoadjuvant Chemotherapy

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## ABSTRACT

### Purpose
To identify clinicopathological factors predictive of distant metastasis in patients who had a pathologic complete response (pCR) after neoadjuvant chemotherapy (NC).

### Methods
Retrospective review of 226 patients at our institution identified as having a pCR was performed. Clinical stage at diagnosis was I (2%), II (36%), IIIA (27%), IIIB (23%), and IIIC (12%). Eleven percent of all patients were inflammatory breast cancers (IBC). Ninety-five percent received anthracycline-based chemotherapy; 42% also received taxane-based therapy. The relationship of distant metastasis with clinicopathologic factors was evaluated, and Cox regression analysis was performed to identify independent predictors of development of distant metastasis.

### Results
Median follow-up was 63 months. There were 31 distant metastases. Ten-year distant metastasis-free rate was 82%. Multivariate Cox regression analysis using combined stage revealed that clinical stages IIIB, IIIC, and IBC (hazard ratio [HR], 4.24; 95% CI, 1.96 to 9.18; $P < .0001$), identification of ≤ 10 lymph nodes (HR, 2.94; 95% CI, 1.40 to 6.15; $P = .004$), and premenopausal status (HR, 3.08; 95% CI, 1.25 to 7.59; $P = .015$) predicted for distant metastasis. Freedom from distant metastasis at 10 years was 97% for no factors, 88% for one factor, 77% for two factors, and 31% for three factors ($P < .0001$).

### Conclusion
A small percentage of breast cancer patients with pCR experience recurrence. We identified factors that independently predicted for distant metastasis development. Our data suggest that premenopausal patients with advanced local disease and suboptimal axillary node evaluation may be candidates for clinical trials to determine whether more aggressive or investigational adjuvant therapy will be of benefit.

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## INTRODUCTION

Neoadjuvant chemotherapy (NC) is the standard therapy for locally advanced breast carcinoma (LABC) and is an increasingly popular treatment strategy for large operable breast cancer. Use of NC was first reported in 1978 as part of a multidisciplinary approach proposed for patients with stage III LABC.[1] Subsequently it was found that NC can provide disease-free survival (DFS) and overall survival (OS) equivalent to those provided by adjuvant chemotherapy.[2,3]

NC has been shown to facilitate breast-conservation therapy,[4] and remains under clinical investigation for several other potential benefits, such as downstaging of primary tumors and lymph nodes, providing

early assessment of response to chemotherapy, and most importantly, obtaining prognostic prognostic/predictive information based on the pathologic response to therapy.[4,5] For example, prospective trials have demonstrated that patients who have a pCR of the primary tumor have significantly improved DFS and OS when compared with patients who do not have a pCR.[2-6,9] Based on these data, a number of groups including our own have used the end point of pCR as a surrogate for OS in the design of clinical trials.

Although a pCR portends a favorable outcome for most patients, some patients with pCR still experience recurrent disease. Reported series have shown 5-year recurrence rates in patients with a pCR ranging from 13% to 25%.[2,6-8]

There currently are no published data examining the predictors of systemic failure after a pCR to neoadjuvant treatment exist. These data would be important to more precisely understand the prognosis of individual patients who achieve a pCR with NC. In addition, the data may identify a small cohort of patients with a poor outcome despite the achievement of pCR. In such patients, pCR may not be a good surrogate of OS, and therefore these patients may not be optimal candidates for clinical trials in which pCR is the primary end point. Finally, such data may also identify patients who may benefit from additional therapy after NC.

## METHODS

### Patients

This was a retrospective study of 226 patients with primary breast carcinoma who had a pCR after receiving NC at The University of Texas M.D. Anderson Cancer Center (Houston, TX) between 1982 and 2002. The M.D. Anderson Cancer Center Surveillance Committee (institutional review board) approved our retrospective review of the patients' medical records for this study. Of 1,451 patients with breast cancer who received NC, 226 (16%) were identified as having a pCR.

Each primary breast tumor was diagnosed by using core-needle biopsy analysis. The clinical stage of the tumors at diagnosis based on the 2003 American Joint Committee on Cancer criteria[10] was I, II, IIIA, IIIB, and IIIC in 2%, 36%, 27%, 23%, and 12% of the patients, respectively. Eleven percent of all patients had inflammatory breast cancer (IBC). Ninety-five percent of the patients received anthracycline-based chemotherapy; 42% of them also received taxane-based therapy either pre- or postoperatively.

### Histopathology

The histologic type of the primary tumors was defined according to the WHO Histological Typing of Breast Tumors.[11] All pathologic tumor specimens were reviewed by breast pathologists at M.D. Anderson. The histologic grade of the tumors was defined according to a modification of Black's nuclear grading system.[12] Immunohistochemical analysis was performed to determine the patients' estrogen-receptor (ER) and progesterone-receptor (PR) status by using standard procedures with 4-$\mu$m sections of paraffin-embedded tissue specimens stained with monoclonal antibodies: 6F11 (Novocastra Laboratories Ltd, Burlingame, CA) for ER and 1A6 (Novocastra Laboratories Ltd.) for PR. Before 1993, the dextran-coated charcoal ligand-binding method was used to determine ER and/or PR status. Nuclear staining in at least 10% of the cells in a section was considered positive for cancer. pCR was defined as no evidence of invasive carcinoma in the breast and axillary lymph nodes at the time of surgery.

### Treatment

Ninety-five percent of the patients received anthracycline-based NC, whereas 5% received taxane-based NC therapy. Twenty-five patients (11%) received four cycles of 1 mg/m$^2$ vincristine, 50 mg/m$^2$ doxorubicin, and 500 mg/m$^2$ cyclophosphamide intravenously on day 1 and 100 mg/m$^2$ prednisone orally on days 1 to 5. Thirteen patients (6%) received three to four cycles of 500 mg/m$^2$ fluorouracil intravenously on day 1, 50 mg/m$^2$ doxorubicin intravenously by continuous infusion over 72 hours on days 1 to 3, 500 mg/m$^2$ cyclophosphamide intravenously on day 1, 1 mg/m$^2$ vincristine intravenously on day 1, and 100 mg/m$^2$ prednisone orally on days 1 to 5. One hundred seventy-two patients (76%) received four to eight cycles of 500 mg/m$^2$ fluorouracil intravenously on days 1 and 4, 50 mg/m$^2$ doxorubicin intravenously by continuous infusion over 72 hours on days 1 to 3, and 500 mg/m$^2$ cyclophosphamide intravenously on day 1 (FAC). Fifteen patients (7%) received 50 mg/m$^2$ doxorubicin intravenously and 75 mg/m$^2$ docetaxel intravenously on day 1. Fifty-nine (26%) patients received 175 to 250 mg/m$^2$ paclitaxel intravenously on day 1 and every 21 days for four cycles or 80 mg/m$^2$ paclitaxel intravenously on day 1 once a week for 12 weeks, followed by four cycles of FAC. Three patients also received neoadjuvant 2 mg/kg trastuzumab intravenously once a week for 24 weeks as part of their primary systemic therapy.

Breast surgery consisted of segmental mastectomy with axillary lymph node dissection (n = 205) when tumor size permitted or modified radical mastectomy according to the judgment of the multidisciplinary care team and patient preference. Sentinel lymph node biopsy alone was performed in 21 cases (9%) as part of an ongoing institutional surgical trial. Patient's who had evidence of multicentric disease were not offered breast-conserving therapy. Sixty-five patients (29%) received adjuvant tamoxifen for 5 years.

Radiotherapy was administered at the completion of primary chemotherapy and after surgery for 197 patients (87%), either because they underwent breast-conservation surgery or had locally advanced disease.

### Statistical Analysis

Data were analyzed separately for all 226 patients and for the 201 patients with no IBC. The log-rank test was used to detect an association between categoric variables and distant metastasis. The minimum, median, and maximum values of the continuous variables were given. The Kaplan-Meier product-limit method was used to compute freedom from distant metastasis. The log-rank test was also used to compare the survival estimates in the two groups. $P$ values $\leq .05$ were considered statistically significant. Cox proportional hazard analysis, which included the factors that had univariate significance, was performed to identify independent factors related to the development of distant metastasis. Recurrence-free survival was measured from the date of first treatment to the date of recurrence or last follow-up visit. Finally, freedom from distant metastasis at 10 years was calculated according to the number of significant factors in the multivariate analysis. Survival analysis was performed with 225 patients because the

only male patient was excluded. Statistical analyses were carried out by using the Statistical Package for the Social Sciences software program (version 12.0; SPSS Inc, Chicago, IL) and Stata statistical Software (Release 8; StataCorp LP, College Station, TX).

## RESULTS

### Patient and Primary Tumor Data

Table 1 summarizes the patient characteristics. The median age of the patients was 46 years (range, 22 to 74 years). The predominant tumor type was invasive ductal carcinoma (89.8%), and the majority of the patients had stage III disease (51.7%). Most of the tumors were ER negative (62.4%) and/or PR negative (53.5%). Her2/*neu* gene amplification status was available in 165 patients, 27% of whom were found to be positive for amplification. Furthermore, 40.7% of the patients underwent breast conservation surgery, 72.0% had more than 10 lymph nodes resected, and 17.0% had residual ductal carcinoma-in-situ in surgical specimens.

### Correlation Between Clinical Variables and Survival

The median follow-up duration was 63 months. Distant metastasis developed in 31 cases. Ten-year actuarial distant metastasis–free rate was 82%. Table 2 shows the results of the univariate analyses for the factors associated with the development of distant metastasis. The associations between distant metastasis and age $\leq$ 50 years ($P = .003$), premenopausal status ($P = .015$), inoperable (stage IIIB, stage IIIC, or inflammatory) disease ($P < .001$), 10 or fewer lymph nodes examined ($P = .0009$), and lymphovascular space invasion ($P = .003$) were statistically significant.

Significant independent predictors for the development of distant metastasis for all patients are summarized in Table 3. Multivariate Cox regression analysis using combined stage revealed that clinical stage IIIB, IIIC and IBC disease (hazard ratio [HR], 4.24; 95% CI, 1.96 to 9.18; $P < .0001$), resection of $\leq$ 10 lymph nodes examined (HR, 2.94; 95% CI, 1.40 to 6.15; $P = .004$), and premenopausal status (HR, 3.08; 95% CI, 1.25 to 7.60; $P = .015$) predicted for distant metastasis. Significant independent predictors for the development of distant metastasis for no-IBC patients are summarized in Table 4. Multivariate Cox regression analysis using combined stage revealed that clinical stage IIIB and IIIC (HR, 3.56; 95% CI, 1.31 to 9.66; $P = .012$), $\leq$ 10 lymph nodes examined (HR, 4.86; 95% CI, 1.77 to 13.34; $P = .002$), premenopausal status (HR, 4.68; 95% CI, 1.06 to 20.77; $P = .042$), and lymphoascular space invasion (HR, 5.36; 95% CI, 1.60 to 17.90; $P = .006$), predicted for distant metastasis.

Figure 1 shows the Kaplan-Meier survival estimates according to the number of independent risk factors. The freedom from distant metastasis at 10 years was 97% for no factors (n = 45), 88% for one factor (n = 102), 77% for two factors (n = 60), and 31% for three factors (n = 14; $P < .0001$ by log-rank test). Figure 2 shows the Kaplan-Meier survival estimates according to the number of independent risk factors. The freedom from distant metastasis at 10 years was 100% for no factors (n = 40), 86% for one to

**Table 1.** Patient Characteristics

| Characteristic | All Patients (N = 226) No. of Patients | % | No-IBC Patients (N = 201) No. of Patients | % |
|---|---|---|---|---|
| Age, years | | | | |
| ≤ 50 | 141 | 62.4 | 125 | 62.2 |
| > 50 | 85 | 37.6 | 76 | 38.8 |
| Menopausal status | | | | |
| Premenopausal | 129 | 57.1 | 115 | 57.2 |
| Postmenopausal | 96 | 42.5 | 85 | 42.3 |
| Sex, male | 1 | 0.4 | 1 | 0.5 |
| Clinical stage | | | 4 | |
| IB | 4 | 1.8 | 35 | 2.0 |
| IIA | 35 | 15.5 | 45 | 17.4 |
| IIB | 45 | 19.9 | 62 | 22.4 |
| IIIA | 62 | 27.4 | 36 | 30.9 |
| IIIB | 36 | 15.9 | 19 | 17.9 |
| IIIC | 19 | 8.4 | | 9.5 |
| Inflammatory | 25 | 11.1 | | |
| Histology | | | | |
| Ductal | 203 | 89.8 | 182 | 90.5 |
| Lobular | 4 | 1.8 | 4 | 2.0 |
| Other | 8 | 3.5 | 8 | 4.0 |
| Unknown | 11 | 4.9 | 7 | 3.5 |
| ER status | | | | |
| Positive | 42 | 18.6 | 38 | 18.9 |
| Negative | 141 | 62.4 | 128 | 63.7 |
| Unknown | 43 | 19.0 | 35 | 17.4 |
| PR status | | | | |
| Positive | 44 | 19.5 | 41 | 20.4 |
| Negative | 121 | 53.5 | 11 | 5.5 |
| Unknown | 61 | 27.0 | 49 | 24.4 |
| Lymphovascular invasion | | | | |
| Yes | 26 | 11.5 | 15 | 7.5 |
| No | 187 | 82.7 | 181 | 86.2 |
| Unknown | 13 | 5.8 | 5 | 2.5 |
| Nuclear grade | | | | |
| 1 | 1 | 0.4 | 0 | 0 |
| 2 | 40 | 17.7 | 33 | 16.4 |
| 3 | 173 | 76.5 | 159 | 79.1 |
| Unknown | 12 | 5.3 | 8 | 4.0 |
| Her2/neu gene amplification status | | | | |
| Positive | 39 | 17.3 | 32 | 15.9 |
| Negative | 53 | 23.5 | 51 | 25.4 |
| Unknown | 134 | 59.3 | 118 | 58.7 |
| Surgery type | | | | |
| Breast conservation | 92 | 40.7 | 92 | 45.8 |
| Mastectomy | 134 | 59.3 | 109 | 54.2 |
| Radiotherapy | | | | |
| Yes | 197 | 87.2 | 172 | 85.6 |
| No | 29 | 12.8 | 29 | 14.4 |

Abbreviation: IBC, inflammatory breast cancer.

**Table 2.** Univariate Analysis for the Factors Associated With the Development of Distant Metastasis

| Characteristic | All Patients (N = 226) | | No IBC Patients (n = 201) | |
|---|---|---|---|---|
| | % of Patients with Distant Metastases | Log-Rank *P* | % of Patients with Distant Metastases | Log-Rank *P* |
| Age, years | | | | |
| < 50 | 18.4 | | 9.5 | |
| > 50 | 5.9 | .003 | 2.0 | .126 |
| Menopausal status | | | | |
| Premenopausal | 19.9 | | 9.0 | |
| Postmenopausal | 6.2 | .015 | 2.5 | .094 |
| Clinical stage | | | | |
| IIIB, IIIC, Inflammatory | 25 | | 7.5 | |
| Operable | 7.5 | < .001 | 4.0 | .002 |
| Histology | | | | |
| Ductal | 12.8 | | 10.0 | |
| Other | 0.0 | .462 | 0.0 | .502 |
| Estrogen receptor | | | | |
| Positive | 11.9 | | 2.0 | |
| Negative | 10.6 | .384 | 5.5 | .469 |
| Progesterone receptor | | | | |
| Positive | 11.4 | | 2.0 | |
| Negative | 10.7 | .669 | 4.5 | .474 |
| Lymphovascular invasion | | | | |
| Yes | 30.8 | | 2.0 | |
| No | 10.7 | .003 | 9.0 | .010 |
| Nuclear grade | | | | |
| 2 | 7.5 | | 2.5 | |
| 3 | 12.7 | .185 | 9.0 | .218 |
| Number of lymph nodes examined | | | | |
| < 10 | 21.7 | | 9.5 | |
| > 10 | 9.9 | .0009 | 7.0 | .097 |
| Radiotherapy | | | | |
| Yes | 13.2 | | 9.0 | |
| No | 17.2 | .243 | 2.5 | .078 |

two factors (n = 140), and 31% for three to four factors (n = 12; $P < .0001$ by log-rank test).

## DISCUSSION

Although only a small percentage of breast cancer patients who achieve a pCR, have a systemic recurrence, we were able to identify three factors that independently predict for distant metastasis. The results of our study indicated that premenopausal patients with stage IIIB breast cancer who have 10 or fewer axillary lymph nodes pathologically examined were more likely to have a poor outcome despite achieving a pCR. In these patients, who made up only 6% of the entire study population, the systemic relapse was 69%.

Prognostic factors for patients receiving NC are different from those for patients who receive adjuvant chemotherapy. Several previous studies of NC addressed clinicopathologic factors associated with outcome in patients with breast cancer. The goal of systemic therapy is to eradicate occult residual distant metastasis to ultimately improve DFS and OS. Theoretically, if a complete response after NC is reflective of sensitivity in occult distant sites, patients who have a pCR in their primary tumor and axillary nodes would have the highest DFS

**Table 3.** Multivariate Cox Regression Analyses for the Factors Associated With the Development of Distant Metastasis: All Patients

| Characteristic | HR | *P* | 95% CI |
|---|---|---|---|
| Premenopausal | 3.08 | .015 | 1.25 to 7.60 |
| Stage IIIB, IIIC, IBC | 4.24 | < .0001 | 1.96 to 9.18 |
| 10 nodes sampled | 2.94 | .004 | 1.40 to 6.15 |

**Table 4.** Multivariate Cox Regression Analyses for the Factors Associated With the Development of Distant Metastasis: Patients Without Inflammatory Breast Cancer

| Characteristic | HR | *P* | 95% CI |
|---|---|---|---|
| Premenopausal | 4.68 | .042 | 1.06 to 20.77 |
| Stage IIIB, IIIC | 3.56 | .012 | 1.32 to 9.66 |
| 10 nodes sampled | 4.86 | .002 | 1.78 to 13.34 |
| Lymphovascular invasion | 5.36 | .006 | 1.60 to 17.90 |

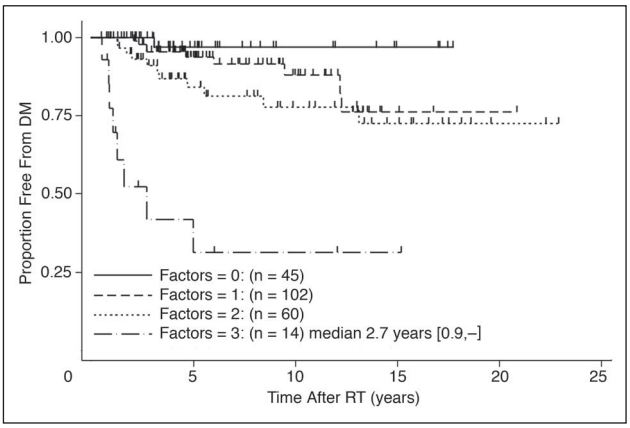


**Fig 1.** Kaplan-Meier survival estimates according to the number of independent risk factors: all patients. DM, distant metastasis; RT, radiotherapy.

rate. This has been demonstrated in studies in which pCR was associated with a better clinical outcome. The most important predictor of long-term outcome is the extent of residual disease on completion of treatment. For example, the absence of residual tumor in the breast and axillary lymph nodes has been shown to be related to improved survival. Specifically, patients who had a pCR after receiving NC had a 5-year OS and DFS rate approaching 90%, whereas those with residual invasive disease had a 5-year OS and DFS rate of 60%.[2,6,8] Identification of patients who will have a pCR in this context has been an important goal in a large number of studies. Also, predictor markers of response have been studied over the past few years.

The axillary lymph node status after NC is an important prognostic factor.[13,14] Specifically, Kuerer et al[13] retrospectively reviewed data for 165 patients with LABC who received treatment in a prospective trial of NC using four cycles of fluorouracil, doxorubicin, and cyclophosphamide. Patients who had a response underwent segmental mastectomy and axillary lymph node dissection or modified radical mastectomy. The patients subsequently received additional chemotherapy followed by irradiation of the breast or chest wall and draining lymphatics. At a median follow-up duration of 35 months, the number of residual metastatic axillary lymph nodes found at axillary dissection was an independent predictor of DFS ($P = .05$). Negative hormonal receptor status has been reported to correlate with increased rates of response to primary chemotherapy.[15] ER-negative tumors are most often associated with a poorly differentiated nuclear grade.[16] Consequently, patients with poorly differentiated tumors have a significantly increased complete response rate and OS.[17] Also, nuclear grade has been found to be associated with cell-cycle proliferative activity as assessed by S phase fraction,[18] and high tumor S phase fraction has been reported to correlate with the response rate.[19] Furthermore, two studies found that the histologic type of the primary tumor seemed to correlate with the probability of response.[20,21] Both studies reported that lobular breast carcinomas responded poorly to primary chemotherapy. Other biologic factors, such as p53, have been studied, but the data are not conclusive because most of the studies were retrospective and had a heterogeneous patient population.

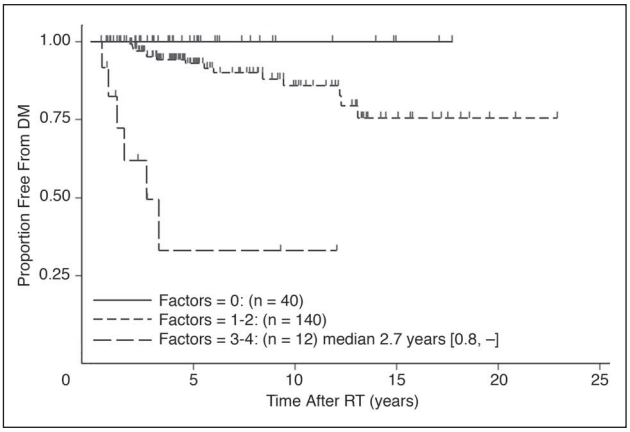


**Fig 2.** Kaplan-Meier survival estimates according to the number of independent risk factors: patients without inflammatory breast cancer. DM, distant metastasis; RT, radiotherapy.

Currently, new methods such as gene expression profiling are being studied for their ability to predict response to primary chemotherapy. Ayers et al[22] reported the discovery of a gene expression profile that predicted pCR after weekly administration of neoadjuvant paclitaxel followed by fluorouracil, doxorubicin, and cyclophosphamide. The overall accuracy of response prediction based on the gene expression profile was 81%, and the positive predictive value of the test for pCR was 75%. In another study, Chang et al[23] analyzed core biopsy specimens obtained from 24 patients with primary breast cancer before treatment. They used cDNA analysis of RNA extracted from the specimens to assess tumor response to neoadjuvant treatment with docetaxel (four cycles at 100 mg/m$^2$ administered daily for 3 weeks). They found differential patterns of expression of 92 genes correlated with response to docetaxel.[23] This 92-gene predictor had a positive and negative predictive value of 92% and 83%, respectively.

Prognostic and predictive factors have been studied in the adjuvant setting to predict survival. Nodal involvement, tumor size, nuclear grade, and hormone receptor status have been described as determinants of recurrence risk.[24] pCR is the most important independent prognostic factor after NC, and the likelihood of pCR is associated with tumor factors such as size, grade, and hormone sensitivity. This association suggests that the underlying biologic factors required for pCR also confer true sensitivity to micrometastatic disease, resulting in long-term improvement in outcome and pCR to chemotherapy, which would help identify patients who have a biologically predetermined excellent prognosis. Although a pCR portends a favorable

outcome in most patients, a significant fraction of patients (13% to 25%) still have recurrent disease.[2,6,7,9]

The present study is the first to address predictive factors for systemic failure after a pCR to NC. We found that premenopausal patients with stage IIIB, IIIC or IBC breast cancer and identification of 10 or fewer axillary lymph nodes are the most likely to have a systemic relapse after having a pCR to NC. Moreover, the freedom from distant metastasis at 10 years was 97% for none of these factors, 88% for one factor, 77% for two factors, and 31% for three factors ($P < .0001$). One more predictive factor was identified when the analysis was performed without the IBC cases. After grouping the risk factor for the no IBC, the freedom from distant metastases at 10 years was 100% for no factors, 86% for one to two factors, and 31% for three to four factors, ($P < .0001$)

The number of positive axillary nodes found in at least a level I and II axillary dissection and with the optimum examination of 10 lymph nodes is an established prognostic factor in the adjuvant setting. As the number of involved lymph nodes increases, the relapse rate increases, and survival rates decrease.[25] In the neoadjuvant setting, persistence of metastatic axillary lymph nodes after treatment is also a prognostic factor for worse outcome.[26] In the present study, we demonstrated that identification of fewer than 10 lymph nodes in the axillary lymph node specimen is independently associated with the risk of developing distant metastases. This finding is consistent with potential understaging of axillary nodal disease. This study does not allow us to specifically discern whether this is due to inadequate removal of pathologically positive lymph nodes, incomplete examination of resected lymph nodes, or a combination of these factors. In fact, we have previously demonstrated that we can identify occult nodal micrometastases with serial histologic sectioning of lymph nodes in approximately 10% of patients who were initially determined to be free of nodal disease.[26] In this regard, the use of sentinel lymph node biopsy following neoadjuvant chemotherapy may be a more accurate staging method based on enhanced routine processing of these lymph nodes.

Age is a prognostic factor in the adjuvant setting, but menopausal status is not as long because some young women have more aggressive forms of breast cancer. Age and menopausal status are closely related, however. In the Early Breast Cancer Trialists' Collaborative Group meta-analysis in 1998, only 10% of women 50 to 69 years old were classified as premenopausal.[27] Also, previously discovered evidence suggests that women younger than 50 years have tumors that overexpress fewer hormone receptors.[28] Our data show that premenopausal women have an increased risk of recurrence after having a pCR independent of their age and hormonal status. We analyzed other parameters used in the adjuvant setting to predict outcome, specifically, age, hormonal status, nuclear grade, *Her2/neu* gene amplification status, lymphovascular invasion, and histologic type, and found no correlation with relapse.

One of the benefits of NC is the possibility of switching to a different regimen if the tumor does not respond. Thomas et al[29] evaluated the use of an alternate non–cross-resistant adjuvant chemotherapy regimen in 193 female patients with breast cancer who had a poor pathologic response to a preoperative doxorubicin-based regimen. Patients with LABC received three cycles of vincristine, doxorubicin, cyclophosphamide, and prednisone (VACP) every 21 days followed by surgery. Patients with less than 1 $cm^3$ of residual tumor at mastectomy received an additional five cycles of VACP. Those with $\geq 1$ $cm^3$ of residual tumor were randomly assigned to receive an additional five cycles of VACP or five cycles of vinblastine, methotrexate with calcium leucovorin rescue, and fluorouracil. The latter patients had a better DFS and OS rate than did those who received additional VACP cycles, although the differences were not statistically significant. Similar results were described in the Aberdeen trial, in which the addition of non–cross-resistant docetaxel to VACP significantly increased 5-year survival.[30]

With the data provided in this study, determining whether to administer further treatment to an identified high-risk group of patients with breast cancer is a good research question. These patients should be candidates for clinical trials, to determine whether more aggressive or investigational adjuvant therapy will be of benefit. By identifying "conventional" risk factors, we may enable large number of community oncologists to participate in new studies of high risk cohorts with pCR.

### *Authors' Disclosures of Potential Conflicts of Interest*

The authors indicated no potential conflicts of interest.

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