The Triple Negative Paradox: Primary Tumor Chemosensitivity of Breast Cancer Subtypes

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Abstract

Purpose: Gene expression analysis identifies several breast cancer subtypes. We examined the relationship of neoadjuvant chemotherapy response to outcome among these breast cancer subtypes.

Experimental Design: We used immunohistochemical profiles [human epidermal growth factor receptor 2–positive (HER2+)/hormone receptor–negative for HER2+/estrogen receptor–negative (ER−), hormone receptor and HER2− for basal-like, hormone receptor–positive for luminal] to subtype a prospectively maintained data set of patients with breast cancer treated with neoadjuvant anthracycline-based (doxorubicin plus cyclophosphamide, AC) chemotherapy. We analyzed each subtype for clinical and pathologic response to neoadjuvant chemotherapy and examined the relationship of response to distant disease–free survival and overall survival.

Results: Of the 107 patients tested, 34 (32%) were basal-like, 11 (10%) were HER2+/ER−, and 62 (58%) were luminal. After neoadjuvant AC, 75% received subsequent chemotherapy and all received endocrine therapy if hormone receptor–positive. The chemotherapy regimen and pretreatment stage did not differ by subtype. Clinical response to AC was higher among the HER2+/ER− (70%) and basal-like (85%) than the luminal subtypes (47%; $P < 0.0001$). Pathologic complete response occurred in 36% of HER2+/ER−, 27% of basal-like, and 7% of luminal subtypes ($P = 0.01$). Despite initial chemosensitivity, patients with the basal-like and HER2+/ER− subtypes had worse distant disease–free survival ($P = 0.04$) and overall survival ($P = 0.02$) than those with the luminal subtypes. Regardless of subtype, only 2 of 17 patients with pathologic complete response relapsed. The worse outcome among basal-like and HER+/ER− subtypes was due to higher relapse among those with residual disease ($P = 0.003$).

Conclusions: Basal-like and HER2+/ER− subtypes are more sensitive to anthracycline-based neoadjuvant chemotherapy than luminal breast cancers. Patients that had pathologic complete response to chemotherapy had a good prognosis regardless of subtype. The poorer prognosis of basal-like and HER2+/ER− breast cancers could be explained by a higher likelihood of relapse in those patients in whom pathologic complete response was not achieved.

Gene expression studies have identified three major subtypes of breast cancer (basal-like, HER2+/ER−, and luminal; ref. 1) that have differing prognoses (2). A particularly poor outcome is seen among the two hormone receptor–negative subtypes (i.e., basal-like and HER2+/ER−), compared with the hormone receptor–high luminal group (2, 3). Evidence suggests that the effect of improved adjuvant chemotherapy is greater among hormone receptor–negative breast cancer (4). A recent report revealed significantly higher pathologic complete response to neoadjuvant chemotherapy among basal-like and HER2+/ER− subtypes compared with luminal subtypes (5). If so, this raises the question of whether the traditional perspective of pathologic complete response as a proxy for relapse and survival holds true across each subtype. In this study, we used immunohistochemistry to classify tumors according to breast cancer subtype and examined the relationship between neoadjuvant response and long-term end points, including distant disease–free survival (DDFS) and overall survival (OS).

Materials and Methods

Patients and treatments. This cohort included patients with stage II and III breast cancer who received neoadjuvant doxorubicin (60 mg/m^2) plus cyclophosphamide (600 mg/m^2) chemotherapy (AC) given i.v. for four cycles, either alone, or as the first component of a sequential

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AC-taxane neoadjuvant regimen. One hundred and seven patients who received neoadjuvant AC and from whom estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and response data were available were identified through the University of North Carolina, Lineberger Comprehensive Cancer Center Neoadjuvant Database, which is a database of all patients treated with neoadjuvant therapy that is updated every 6 months and includes serial clinical, radiographic, and pathologic tumor measurements, treatment details, and outcome. Patients included in this data set were treated between June 1998 and October 2003.

Molecular classification. The best way to perform breast tumor intrinsic subtyping is to use microarrays for gene expression analysis, however, most archived clinical specimens are not amenable to microarray analysis and other methods must be employed. We previously showed that a combination of immunohistochemical markers could be used for molecular subtyping (6). A combined analysis of the data presented in Nielsen et al. (6) and Livasy et al. (7) on the subset of samples in which we had both gene microarray data and immunohistochemistry for ER and HER2 revealed that the basal-like subtype was largely ER− (32 of 34) and HER2− (all 34), the HER2+/ER− subtype was ER− (all 12) and HER2+ (11 of 12), and the luminal subtype (luminal A and B combined) was ER+ (24 of 24); thus, on this combined set of 70 tumors, 94% of basal-like, 92% of HER2/ER−, and 100% of luminal tumors would have been correctly identified using a simple ER and HER2 scoring method. For this study, we used these immunohistochemical surrogates taken from the clinical data and defined the basal-like subtype as ER−, PR−, and HER2−, the HER2+/ER− subtype as ER−, PR−, and HER2+, and the luminal A and B subtypes were combined into a single luminal group defined by either ER or PR positivity, regardless of other characteristics. In hierarchical clustering analyses, there are at least two subgroups of luminal breast cancers, i.e., luminal A and B. Because hormone receptor–positive/HER2+ tumors are generally luminal B (2, 3), we have also analyzed them subcategorized as luminal B here, as was done in a previous publication (8); hormone receptor–positive/HER2− tumors are designated as luminal A. However, it is important to recognize that hormone receptor–positive/HER2+ tumors comprise a minority of luminal B, so this method of subcategorizing the luminal subtypes will necessarily misclassify a substantial fraction of luminal B tumors into the luminal A category. The ER and PR were scored positive at University of North Carolina if at least 5% of the invasive cells showed staining. HER2 immunohistochemistry used CB11 antibody until 1998, until the DAKO Herceptest was used (DAKO, Carpinteria, CA). Prior to 2000, HER2 was scored positive if a 2+ or 3+ result was found, after 2000, a 2+ result was only positive if confirmed by fluorescence *in situ* hybridization for gene amplification.

Clinical response and statistical methods. Clinical response was measured according to the Response Evaluation Criteria in Solid Tumors (9). In those patients with tumors that were clinically difficult to measure, radiographic response to therapy was substituted for clinical response. In all patients, only one method of tumor measurement was used. Whenever possible, tumor measurements were obtained from the same physician. Pathologic response to chemotherapy was assessed by posttreatment American Joint Committee on Cancer tumor-node-metastasis staging for invasive carcinoma only (10).

Fisher exact test was used to evaluate possible associations between subtypes and the nominal and dichotomized covariates (i.e., race, dose density, and whether or not adjuvant endocrine therapy was given, etc.). When at least one of the comparing variables was ordinal (such as stage of disease, clinical, and pathologic response), the nonparametric Jonckheere-Terpstra method was used to test for ordered differences among categories. With this test, the null hypothesis is that the distribution of the response does not differ across ordered categories. The Kruskal-Wallis test (using Van der Waerden normal scores) was used to evaluate possible differences in responses between subtypes and the continuous covariate of age. Logistic regression was used to evaluate the association of age, race, disease stage, HER2+/ER− versus luminal subtypes, and basal-like versus luminal subtypes with clinical response (complete response or partial response versus *not* complete response or partial response).

Two types of time-to-event analyses were done: DDFS and OS. DDFS was calculated as the time from the date of diagnosis of the primary tumor to the date of the development of distant or regional metastases, date of death from any cause, or the date of last contact. This definition of DDFS did not include recurrences in a conserved breast, the axilla, or on the chest wall. OS was calculated as the time from the date of diagnosis of the primary tumor to the date of death from any cause, or the date of last contact. The Kaplan-Meier (or product limit) method was used to estimate the DDFS and OS survivorship functions. The Wilcoxon method (also known as the Gehan or Breslow test) was used to compare time-to-event curves. This test was chosen because of the way it is calculated; it places more emphasis on earlier differences between curves. Statistical analyses were done using JMP version 5 and SAS Statistical Software, version 9.1, both products of the SAS Institute, Inc. (Cary NC). This study was approved by the University of North Carolina at Chapel Hill Committee on the Protection of the Rights of Human Subjects.

Results

Patient and tumor characteristics. Table 1 shows the characteristics of the patients in this study. Patients with basal-like, HER2+/ER−, and luminal subtypes of breast cancer did not differ significantly by age, race, or disease stage ($P = 0.17$, $P = 0.15$, and $P = 0.56$, respectively). All patients received AC neoadjuvant chemotherapy at conventional doses for four cycles. Twenty-eight (26%) received AC on a dose-dense schedule (every 2 weeks), whereas the rest of the patients received AC on an every 3 weeks schedule. The use

Table 1. Patient characteristics

	All patients	Basal-like	HER2+/ER	Luminal B*	Luminal A	*P*
N (%)	107	34 (32%)	11 (10%)	26 (24%)	36 (34%)	
Median age (range)	51 (27-79)	45 (27-69)	49 (30-79)	51.5 (32,77)	52.5 (31,64)	0.17
Race						
African-American	36 (34%)	16 (47%)	5 (45%)	5 (19%)	10 (28%)	0.15
Caucasian	68 (63%)	17 (50%)	6 (55%)	21 (81%)	24 (67%)	
Other	3 (3%)	1 (3%)	0	0	2 (5%)	
Stage II	42 (39%)	12 (35%)	3 (27%)	10 (38%)	17 (47%)	0.26
Stage III	65 (61%)	22 (65%)	8 (73%)	16 (62%)	19 (53%)	

*ER+ or PR+, HER2+.

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Table 2. Breast cancer phenotype and clinical response to anthracycline-based chemotherapy

	Entire population	Basal-like (n = 34)	HER2* (n = 11)	Luminal B (n = 26)	Luminal A (n = 36)	P
Clinical response to AC						
Complete response	15 (14%)	10 (29%)	1 (10%)	2 (8%)	2 (6%)	<0.0001
Partial response	50 (47%)	19 (56%)	6 (60%)	13 (50%)	12 (33%)	
Stable disease	40 (38%)	5 (15%)	3 (30%)	11 (42%)	21 (58%)	
Progressive disease	1 (1%)	0	0	0	1 (3%)	
Complete response + partial response	65 (61%)	29 (85%)	7 (70%)	15 (58%)	14 (39%)	<0.0001
Pathologic stage post-chemotherapy						0.0004
0	17 (16%)	9 (27%)	4 (36%)	4 (15%)	0	
I	26 (25%)	10 (31%)	1 (9%)	8 (31%)	7 (21%)	
II	33 (32%)	8 (24%)	5 (46%)	8 (31%)	12 (35%)	
III	27 (26%)	6 (18%)	1 (9%)	5 (19%)	15 (44%)	
IV	1 (1%)	0	0	1 (4%)	0	

*One patient with the HER2+/ER− subtype was not evaluable for clinical response, and three patients did not undergo primary surgery.

of the dose-dense schedule did not differ among tumor subtypes (P = 0.46). Most patients (80 of 107, 75%) received additional neoadjuvant chemotherapy following AC, which primarily involved either paclitaxel or docetaxel (79 of 80, or 99%). One patient received only one cycle of taxane, which was poorly tolerated, and completed the remainder of her post-AC chemotherapy with vinorelbine. It is worth noting that clinical response rates reflect only the AC contribution, whereas pathologic response rates reflect both the AC and subsequent neoadjuvant regimens. Adjuvant endocrine therapy was given to 3 of 34 (9%) patients with basal-like, 0 of 11 patients with HER2+/ER−, and 61 of 62 (98%) patients with luminal tumor (P < 0.0001) subtypes.

Clinical and pathologic response to neoadjuvant anthracycline. Table 2 illustrates the clinical response to AC, and the pathologic response to all neoadjuvant therapies. Clinical response assessments were done after AC and did not reflect the effect of subsequent sequential drugs. Clinical response to AC differed significantly among the subtypes (P < 0.0001), with HER2+/ER− and basal-like subtypes showing higher clinical response rates than luminal subtypes. This difference remained when evaluating a collapsed table comparing the dichotomized proportion of complete and partial responses to the rest (P < 0.0001). The greatest difference was seen between luminal A (39%) and basal-like (85%) subtypes. Logistic regression was used to evaluate the association of age, race, disease stage, HER2+/ER− versus luminal subtype, and basal-like versus luminal (A + B combined) subtypes relative to clinical response (complete response or partial response versus *not* complete response or partial response); of these, only basal-like versus luminal was significant (odds ratio, 6.6; 95% confidence interval, 2.26-19.28).

As mentioned above, most patients received subsequent taxane-based chemotherapy after AC that would not contribute to the clinical response, but may have contributed to the pathologic response. Patients who were stage II (20 of 42, 48%) were significantly more likely to receive AC alone than stage III (7 of 65, 11%; P < 0.0001). Additional chemotherapy was received by 26 of 34 (76%) patients with basal-like tumors, 10 of 11 (90%) HER2+/ER−, and 44 of 62 (71%) with luminal tumors (21 of 26 luminal B, and 23 of 36 luminal A). These differences were not significant. Three of the patients did not undergo primary surgery and thus do not have pathologic data available. Pathologic complete response was higher in those that received subsequent chemotherapy (16 of 79, 20%) than those that did not (1 of 25, 4%; P = 0.04); the use of subsequent chemotherapy was discretionary, which limits the interpretability of this

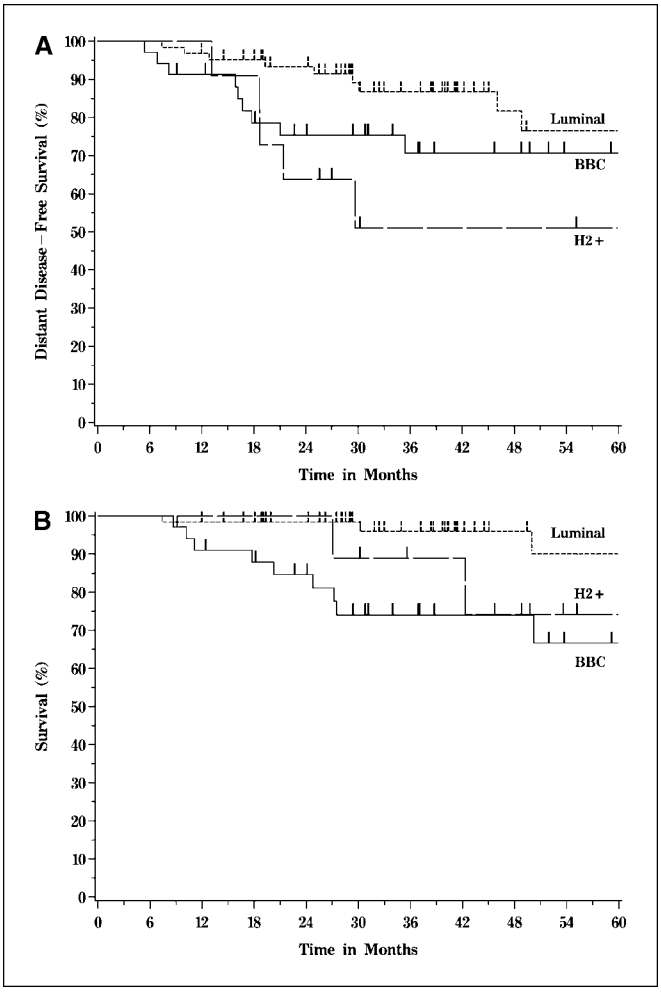

Fig. 1. DDFS (*A*) and OS (*B*) according to breast cancer subtype.

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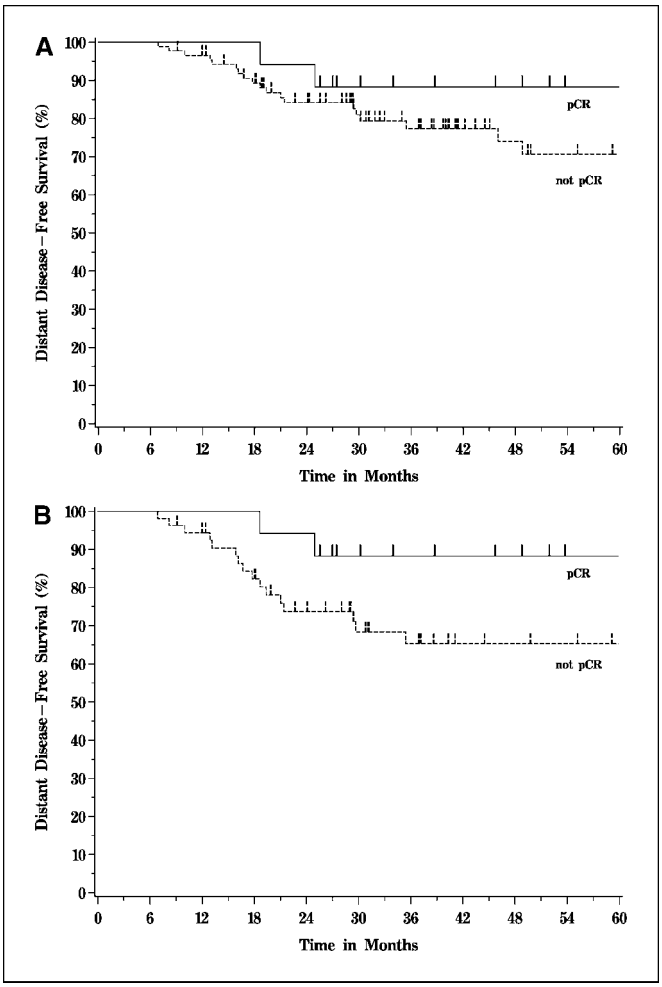

Fig. 2. DDFS of the entire cohort comparing those patients that achieved pathologic complete response and those that had residual disease after neoadjuvant anthracycline-based chemotherapy. Regardless of subtype, only two relapses occurred among those with pathologic complete response to neoadjuvant chemotherapy at 39 mo of follow-up ($P = 0.30$; *A*). DDFS of the cohort excluding luminal A illustrates the relationship between pathologic complete response and outcome among those most affected by chemotherapy ($P = 0.09$; *B*).

difference. Pathologic complete response to chemotherapy was significantly better among basal-like (27%) and HER2+/ER− (36%) subtypes versus the combined luminal subtypes (7%; $P = 0.01$). Four of 26 (15%) luminal B tumors had pathologic complete response, but there were no pathologic complete responses among 34 patients with luminal A tumors that underwent surgery ($P = 0.03$). In addition, the percentage of patients with minimal residual disease (stage 0-I) after chemotherapy was higher among basal-like (19 of 33, 58%) than HER2+/ER− (5 of 11, 45%) or luminal subtypes [luminal B (12 of 26, 46%) and luminal A (7 of 34, 21%); $P = 0.002$].

Long-term end points. The median follow-up time for the survivors in this cohort was ~39 months. In this patient set, 21 (20%) relapsed and 19 (18%) died, and there were 23 alive more than 5 years from diagnosis. The Kaplan-Meier method was used to estimate time-to-event functions. Figure 1 illustrates a significant difference in DDFS ($P = 0.04$) and OS ($P = 0.02$) among the subtypes (results were similar when obtained whether classified as three groups or four groups with luminal A and B categories). The estimated 4-year DDFS (with 95% confidence limits) were: basal-like, 71% (51-84%); HER2+/ER−, 51% (18-77%); and luminal (A + B combined), 82% (64-91%); with luminal A being, 84% (52-95%); and luminal B being, 78% (54-90%). As illustrated in Fig. 1, the difference between subtypes was particularly apparent early; all the relapses after 40 months occurred in only the luminal cancers. Only 2 of the 17 patients (one with the HER2+/ER− subtype, one with the luminal B subtype) with pathologic complete response to neoadjuvant chemotherapy relapsed, and none died (Fig. 2; $P = 0.30$). To further examine the relationship between outcome and pathologic complete response, we tested the outcomes of the subtypes after removing all patients that achieved a pathologic complete response and determined that a poorer outcome was seen among the basal-like and HER2+/ER− subtypes compared with luminal subtypes; this seems to be due to a greater likelihood of relapse or death among those with residual disease following neoadjuvant chemotherapy ($P = 0.003$; Fig. 3).

The most common site of initial relapse was bone, which was involved in 9 of 20 (45%) patients. Other sites (in order of frequency) included: lymph nodes (4, 20%), central nervous system (4, 20%), lung or pleura (2, 10%), and liver (1, 5%).

Discussion

Gene expression analyses have identified molecular subtypes that are refining our understanding of breast cancer biology. The luminal subtypes make up the vast majority of the hormone receptor–positive tumors, whereas the basal-like and HER2+/ER− subtypes make up the majority of hormone receptor–negative cancers. The poor outcomes seen among basal-like and HER2+/ER− subtypes has been reported previously (2, 3); however, it has not been clear if this poor outcome was due their biology, or resistance to systemic therapy, or some combination of the two.

Response to neoadjuvant chemotherapy was related to subsequent disease-free and overall survival (10–12), thus

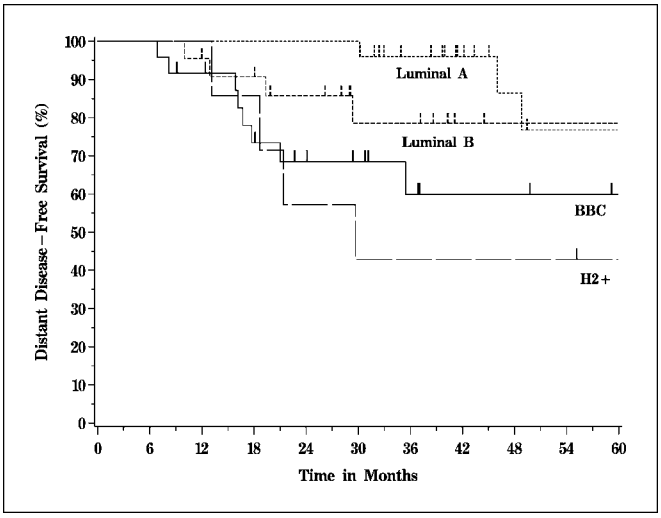

Fig. 3. DDFS among those patients with residual disease after neoadjuvant chemotherapy by breast cancer subtype. If pathologic complete response was not achieved, basal-like and HER2+/ER− subtypes had a higher risk of subsequent relapse compared with the luminal subtypes.

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making this a valuable intermediate end point for the evaluation of novel agents or combinations. We examined whether this end point varied by subtype in the presence of neoadjuvant chemotherapy and determined that the luminal subtypes had a significantly lower clinical and pathologic response relative to the basal-like and HER2+/ER− subtypes. Despite higher chemosensitivity to conventional anthracycline-based chemotherapy, the basal-like and HER2+/ER− subtypes still showed worse survival due to higher relapse among those with residual disease after chemotherapy.

Previous reports have suggested that ER+ tumors have a poorer response to primary chemotherapy than ER− tumors (13, 14). In a study limited to ER+ tumors only, the pathologic complete response rate to combination anthracycline and taxane neoadjuvant chemotherapy was a mere 7% (15), which was similar to the frequency in the combined luminal A + B (hormone receptor – positive) tumors observed here. A different anthracycline-taxane regimen in HER2-overexpressing tumors, whether ER+ or ER−, revealed a pathologic complete response rate of 25% (16). That study included both hormone receptor – negative tumors (HER2+/ER− subtype) and hormone receptor – positive tumors (luminal B subtype here). A recently reported study using gene expression profiling and a similar molecular classification that was used here also showed that both basal-like and HER2+/ER− subtypes have high pathologic response to therapy (5). Our study, using immunohistochemical proxies for the subtypes, confirms these findings and extends them through the use of long-term end points to explain the paradox of better pathologic complete response rates but worse survival driven by higher relapse rates among those tumors that were not eradicated by the chemotherapy.

There are multiple potential reasons that the response to chemotherapy differed by subtype. The basal-like and HER2+/ER− breast cancer subtypes are characterized by the high expression of the proliferation cluster of genes (2), which is mirrored by other more conventional indexes of proliferation as well. A prognostic index that is heavily influenced by proliferation genes was recently shown to predict pathologic complete response to doxorubicin/docetaxel primary chemotherapy (17), lending credence to the relationship of proliferation to chemosensitivity.

The paradox of higher sensitivity to neoadjuvant anthracycline in subtypes known to have a poor prognosis is explained by the high relapse among those with residual disease. Reassuringly for clinical trial designs that use pathologic complete response as an intermediate end point, the relationship of pathologic complete response to survival was maintained across patients and subtypes in this study. Specifically, among those with complete pathologic complete response, the patients continued to do well and almost all remained disease-free. However, of those with residual disease, early relapse and death were more frequent among the basal-like and HER2+/ER− subtypes. This may well reflect the importance of the adjuvant endocrine therapy that most luminal tumors received and most basal-like and HER2+/ER− did not. Thus, it may be easier to achieve pathologic complete response in basal-like and HER2+/ER− tumors, but if pathologic complete response is not achieved, they are more likely to relapse early and die. This is in keeping with the emerging understanding that advances in chemotherapy primarily affect relapses within the first few years after diagnosis (4), which is when the fast-growing ER− subtypes are more likely to relapse. Our finding of particularly poor outcome in basal-like and HER2+/ER− subtypes with residual disease after chemotherapy supports efforts to further improve these outcomes and suggests that continued treatments may be necessary. It is reasonable to assume that trastuzumab will shift the HER2+/ER− subtype survival curves upward (18 – 20); however, we still lack targeted therapies for the basal-like patients. Interestingly, although this study is not large enough for direct comparisons within the luminal subtypes, the clinical and pathologic response to chemotherapy was higher in the luminal B subtype defined by both hormone receptor and HER2 expression than in the luminal A subtype. Given the low proportion of luminal A tumors that achieve pathologic complete response, it is possible that this is a less useful intermediate end point for outcome among luminal A tumors compared with other subtypes. Luminal B tumors virtually always have high recurrence scores (21), which is a gene expression – based model that is associated with chemosensitivity (17, 22).

There are caveats to this study. The entire patient set received four cycles of AC as initial neoadjuvant therapy; however, the majority received additional neoadjuvant chemotherapy that primarily included paclitaxel. Thus, although the clinical response rates were not affected, the pathologic responses reflect the effects of the entire chemotherapy regimen. Because the chemotherapy regimen did not statistically differ by subtype and the findings were consistent across clinical and pathologic responses, these differences in treatment should not confound our primary findings. However, it should be taken into account when considering the pathologic response rate. Another potential caveat to the generalizability of these findings is with regards to HER2+ patients. At the time of this study, there was a clinical trial incorporating trastuzumab into neoadjuvant therapy at the University of North Carolina. Because the inclusion of a biological therapy would confound the clinical and pathologic response assessments, all of those patients were excluded from this report. It is possible that patients at higher risk would be more likely to participate in such a trial, thereby biasing our HER2+ cohort to lower risk tumor. We do not believe that this significantly affected our results because we did not see a difference in tumor stage at presentation by subtype, and because our results were qualitatively similar to those of Rouzier and colleagues in this respect (5). The exclusion of trastuzumab-treated patients, however, certainly decreased the size of the HER2+ cohort included in this study.

In summary, we have found that patients with the basal-like and HER2+/ER− subtype of breast cancer have higher sensitivity to neoadjuvant anthracycline-based chemotherapy than the luminal subtype, and have higher rates of pathologic complete response. Those patients who achieved a pathologic complete response had a highly favorable outcome. However, despite this sensitivity, the basal-like and HER2+/ER− subtypes still showed the same poor prognosis as others have found before, with high relapse rates among those who did not achieve pathologic complete response. Targeted treatment analogous to endocrine therapy for luminal/ER+ patients is needed for these two subtypes. We now have such a treatment for patients with the HER2+/ER− subtype (18 – 20), but not for patients with the basal-like breast cancer subtype.

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