Original Research

# Pathologic Complete Response After Neoadjuvant Chemotherapy and Long-Term Outcomes Among Young Women With Breast Cancer

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## Abstract

**Purpose:** Breast cancer in young women is associated with an aggressive tumor biology and higher risk of recurrence. Pathologic complete response (pCR) after neoadjuvant therapy has been shown to be a surrogate marker for disease-free survival (DFS) and overall survival (OS), but the association between pCR and survival outcomes in young women with breast cancer is not well described. **Methods:** This study included women aged ≤40 years at diagnosis who received neoadjuvant chemotherapy (NAC) for stage II–III invasive breast cancer between 1998 and 2014 at Massachusetts General Hospital. Outcomes were compared between patients who achieved pCR (ypT0/is, ypN0) and those with residual disease. **Results:** A total of 170 young women were included in the analytical data set, of which 53 (31.2%) achieved pCR after NAC. The 5-year DFS rate for patients with and without pCR was 91% versus 60%, respectively ($P$<.01), and the OS rate was 95% versus 75%, respectively ($P$<.01). Among patients with pCR, no difference was seen in OS irrespective of baseline clinical stage ($P$=.6), but among patients with residual disease after NAC, a significant difference in OS based on baseline clinical stage was observed ($P$<.001). **Conclusions:** Our results suggest pCR after NAC is strongly associated with significantly improved DFS and OS in young women with breast cancer, and perhaps even more so than baseline stage. However, the significantly higher mortality for patients who did not attain pCR highlights the need for better therapies, and the neoadjuvant trial design could potentially serve as an efficient method for rapid triage and escalation/de-escalation of therapies to improve outcomes for young women with breast cancer.

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Although breast cancer in young women is rare overall, it accounts for a significant proportion of all cancers in women aged ≤40 years.[1] It is estimated that in 2015, 5% of all new invasive breast cancer cases and 3% of all breast cancer deaths in the United States occurred in women aged <40 years.[2] Although young women are more likely to receive more intensive therapy, young age has been shown to be a risk factor for breast cancer recurrence and death.[3] A recent study based on data from 8 NCCN Member Institutions between January 2000

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and December 2007 showed that women aged ≤40 years at diagnosis had greater breast cancer mortality (hazard ratio, 1.4; 95% CI, 1.2–1.7), with luminal breast cancer being most prognostic for increased risk of death in this age group.[4]

Multiple factors contribute to greater breast cancer mortality among young women with breast cancer. Routine breast cancer screening is not recommended for women <40 years of age unless they are at elevated risk. Thus, women in this age group are more likely to present with a palpable mass. In addition to being more likely to present at a later stage, young women have also been shown to be more likely to have an aggressive biological subtype of breast cancer compared with older women.[5–7] Age-related differences in key breast cancer genes for proliferation, invasion, and metastasis have been reported.[8] Thus, there is a critical need to identify novel actionable targets and develop robust therapies for young women with breast cancer.

Neoadjuvant chemotherapy (NAC) is being increasingly used in the management of localized breast cancer as an alternative to adjuvant chemotherapy. Studies have shown that the benefit of chemotherapy is similar when given in the adjuvant and neoadjuvant settings, with no difference in survival.[9,10] However, NAC offers several additional advantages from both a clinical and a research perspective. In patients with large tumors, NAC has the potential to reduce tumor size to improve the rate of breast conservation surgery (BCS) and can lead to less extensive axillary surgery.[11] Because the primary tumor remains intact during therapy, the neoadjuvant treatment approach allows for monitoring of treatment response. Advantages include the discontinuation of inactive therapy in the event of disease progression, thereby saving the patient exposure to potentially toxic therapy. The neoadjuvant platform is also recognized as a human in vivo system to explore predictive biomarkers, surrogate end points, and the efficacy of novel therapies.[11]

Pathologic complete response (pCR) after NAC has been shown to be a surrogate marker for disease free-survival (DFS) and overall survival (OS), and, from a research perspective, offers an efficient mechanism to explore predictive biomarkers and triage novel agents.[11–14] However, the prognostic significance of pCR after NAC has been somewhat controversial, and its surrogacy for long-term outcomes is much less studied in younger women.[15] A pooled study of 8 prospective randomized trials of NAC conducted in Germany compared a subgroup of 1,453 women aged <40 years versus women aged 40 to 49 years and those aged ≥50 years.[16] This study found that the pCR rate was significantly higher in the group aged <40 years compared with those aged 40 to 49 years and ≥50 years (20.9 vs 17.7 vs 13.7%; $P<.001$), but in the overall study population, recurrence and survival were significantly worse for women aged <40 years.[16] Several important scientific questions remain regarding whether pCR after NAC is a valid surrogate marker for outcomes in young women with breast cancer, including whether results vary by subtype of breast cancer. The primary objective of this study was to determine the association between pCR and long-term outcomes among a cohort of young women with breast cancer.

## Methods

### Patient Selection

An Institutional Review Board–approved retrospective review was conducted of all women aged ≤40 years at diagnosis who received NAC (plus trastuzumab if indicated) and surgery for clinical stage II–III invasive breast cancer between 1998 and 2014 at Massachusetts General Hospital. Patients were excluded if part of their care was received elsewhere and sufficient details were unavailable.

### Data Collection and End Points

Clinicopathologic data and recurrence data were retrospectively collected from the electronic medical record. Survival data were gathered from the combined use of the medical record, state tumor registry, death certificate data, and Social Security Death Master File. Survival end points were DFS and OS. A DFS event included any local or distant recurrence. Tumor biology was categorized as hormone receptor (HR)–positive, HER2-positive, or triple-negative breast cancer (TNBC). The cutoff values for estrogen receptor (ER) and progesterone receptor (PR) were ≥1% positive nuclei. HER2 was assessed at diagnosis for all patients at our institution using standard immunohistochemistry, as well as fluorescence in situ hybridization when indicated, using standard criteria at the time, including ASCO/College of American Pathologists guidelines beginning

in 2007. pCR was defined as no residual invasive disease in the breast and axilla, with noninvasive residuals permitted, including ductal carcinoma in situ (ypT0/is ypN0), as per FDA guidance.[17]

### Statistical Analysis

Descriptive statistics were used to describe baseline characteristics. Logistic regression was used to evaluate association of clinicopathologic factors with pCR. Cox regression analyses were conducted to evaluate the association of chemotherapy response and outcomes. DFS and OS were calculated from date of diagnosis to event or last follow-up and presented as Kaplan-Meier curves. The actuarial comparison of groups was based on a log-rank test. Figures 1 through 4 represent unadjusted analyses. Statistical significance was defined as a *P* value <0.05. STATA 14 (StataCorp LP, College Station, TX) was used to perform analyses.

## Results

A total of 170 women aged ≤40 years treated with systemic NAC (plus trastuzumab if indicated) for invasive breast cancer from 1998 through 2014 were included in the analytical data set. Baseline patient characteristics are shown in Table 1. Most patients had grade 3 (71.2%), clinical stage II (70%), invasive ductal carcinoma (93.5%). Subtypes based on receptor status revealed that 39% of patients were HR-positive/HER2-negative, 32% were HER2-positive, and 28% had TNBC. Of the 55 HER2-positive patients, 89.1% received neoadjuvant trastuzumab. Among the 143 patients who had germline genetic testing performed, 25 (17.5%) had a pathogenic mutation, with *BRCA1* being the most common (n=16).

### Factors Associated With pCR

Pathologic staging after NAT is outlined in supplemental eTable 1 (available with this article at JNCCN.org). Among 170 patients, 53 (31.2%) had a pCR (breast and axilla). The occurrence of pCR was significantly higher among patients with HER2-positive (47.3%) and TNBC (39.6%) subtypes compared with those with HR-positive/HER2-negative (11.9%) breast cancer (*P*<.001).

The association between pCR and select clinicopathologic factors is shown in Table 2. In a multi-

**Table 1. Patient Characteristics (N=170)**

| | N | % |
|---|---|---|
| Median age at diagnosis (range), y | 36 (24–40) | NA |
| Clinical stage (AJCC 7th edition) | | |
| IIA | 47 | 27.6 |
| IIB | 72 | 42.4 |
| IIIA | 38 | 22.4 |
| IIIB | 7 | 4.1 |
| IIIC | 6 | 3.5 |
| Tumor histology | | |
| Invasive ductal carcinoma | 159 | 93.5 |
| Invasive lobular carcinoma | 4 | 2.4 |
| Mixed invasive ductal/lobular carcinoma | 4 | 2.4 |
| Other | 3 | 1.8 |
| Grade | | |
| 1 | 1 | 0.6 |
| 2 | 48 | 28.2 |
| 3 | 121 | 71.2 |
| Receptor status | | |
| HR+/HER2– | 67 | 39.4 |
| HER2+/HR+ | 34 | 20.0 |
| HER2+/HR– | 21 | 12.4 |
| TNBC | 48 | 28.2 |
| Germline mutation status | | |
| *BRCA1*+ | 16 | 9.4 |
| *BRCA2*+ | 6 | 3.5 |
| Li-Fraumeni (*p53*) | 2 | 1.2 |
| *CHEK2* | 1 | 0.6 |
| Negative | 118 | 69.4 |
| No genetic testing performed | 27 | 15.9 |
| Family history of breast cancer | | |
| Yes | 70 | 41.2 |
| No | 100 | 58.8 |
| Category of neoadjuvant chemotherapy | | |
| Anthracycline & taxane-based | 108 | 63.5 |
| Anthracycline-based only | 18 | 10.6 |
| Taxane-based only | 21 | 12.4 |
| Platinum-containing | 23 | 13.5 |
| Use of neoadjuvant HER2-directed therapy | | |
| Yes | 49 | 28.8 |
| No | 6 | 3.5 |
| Not applicable (HER2–) | 115 | 67.6 |
| Type of breast surgery | | |
| Mastectomy | 105 | 61.8 |
| Lumpectomy | 65 | 38.2 |
| Prophylactic contralateral mastectomy | | |
| Yes | 64 | 37.7 |
| No | 41 | 24.1 |
| Not applicable | 65 | 38.2 |
| Adjuvant radiation | | |
| Yes | 140 | 82.4 |
| No | 30 | 17.6 |
| Adjuvant chemotherapy | | |
| Yes | 54 | 31.8 |
| No | 116 | 68.2 |
| Adjuvant anti-HER2 therapy | | |
| Yes | 51 | 30.0 |
| No | 4 | 2.4 |
| Not applicable (HER2–) | 115 | 67.6 |
| Adjuvant endocrine therapy | | |
| Yes | 94 | 55.3 |
| No | 7 | 4.1 |
| Not applicable (HR–) | 69 | 40.6 |
| Adjuvant ovarian suppression | | |
| Yes, BSO | 19 | 11.2 |
| Yes, medically induced | 21 | 12.4 |
| No | 61 | 35.9 |
| Not applicable (HR–) | 69 | 40.6 |

Abbreviations: BSO, bilateral salpingo-oophorectomy; HR, hormone receptor; NA, not applicable; TNBC, triple-negative breast cancer.

**Table 2. Association of Clinicopathologic Factors With Pathologic Complete Response**

| | Univariate Analysis | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|
| Factor | OR | 95% CI | *P* Value | OR | 95% CI | *P* Value |
| Age at diagnosis (≤40 years) | 0.94 | 0.87–1.02 | .15 | 0.94 | 0.85–1.02 | .15 |
| Clinical stage III vs II | 0.43 | 0.20–0.95 | .036 | 0.40 | 0.17–0.96 | .04 |
| Grade 3 vs grade 1/2 | 7.66 | 2.59–22.66 | <.001 | 5.90 | 1.85–18.88 | .003 |
| TNBC vs HR+/HER2– | 4.83 | 1.89–12.35 | .001 | 2.70 | 0.98–7.45 | .056 |
| HER2+ vs HR+/HER2– | 6.61 | 2.67–16.40 | <.001 | 4.98 | 1.80–13.73 | .002 |
| Anthracycline + taxane vs other regimens | 1.53 | 0.79–2.98 | .21 | 0.93 | 0.43–2.03 | .85 |

Abbreviations: HR, hormone receptor; OR, odds ratio; TNBC, triple-negative breast cancer.

variate model, significant predictors of pCR included baseline clinical stage, tumor grade, and HER2 status. Most patients received anthracycline/taxane-based chemotherapy, with no significant association seen between pCR and type of chemotherapy received. Among patients with any germline pathogenic mutations, 56% had pCR. Occurrence of pCR among *BRCA* mutation carriers was 50% (8 of 16) for *BRCA1* and 66.7% (4 of 6) for *BRCA2*. Among *BRCA* carriers with pCR, 8 had TNBC, 2 had HR-positive/HER2-negative tumors, and 2 had HER2-positive tumors.

### Association of pCR and Recurrence

Over a median follow-up of 5.2 years, 50 of 170 patients (29.4%) experienced a recurrence, 6 of which were local recurrences only (all patients without pCR). Median time to any recurrence was 2 years (range, 0.5–8.3 years). Only 3 recurrences (5.7%; all distant) occurred among the 53 patients with pCR, whereas 47 recurrences (40.2%) occurred among the 117 patients without pCR (*P*<.001).

Achievement of pCR was associated with significantly improved DFS (hazard ratio, 0.12; 95% CI, 0.04–0.39; *P*<.001; Figure 1). The 5-year DFS rate for patients with pCR was 91% versus 60% for those without pCR. Patients with pCR after NAC had significantly improved DFS in all 3 subtypes based on receptor status (Figure 2). Among all patients, no significant difference in DFS was seen based on category of NAC received (supplemental eFigure 1).

### Association of pCR and Survival

Among 170 patients, 39 (22.9%) died during the study period; 3 deaths (5.7%) occurred among the 53 patients with pCR, whereas 36 deaths (30.8%) occurred among the 117 patients without pCR (*P*=.002). Achievement of pCR was associated with significantly improved OS (hazard ratio, 0.19; 95% CI, 0.06–0.62; *P*=.006; Figure 3). The estimated 5-year OS rate for patients with pCR was 95% versus 75% for those without pCR.

Patients with pCR after NAC had better OS in all 3 breast cancer subtypes based on receptor status (supplemental eFigure 2). In the absence of pCR, OS was significantly worse among patients with stage III disease compared with those with stage II disease (*P*<.001; Figure 4). However, among patients with pCR, no significant difference was seen in OS based on clinical stage (*P*=.60; Figure 4).

## Discussion

Our results suggest that pCR after NAC is associated with significantly better OS (95% estimated 5-year OS rate) in young women with breast cancer compared with those without pCR (75%). The occurrence of pCR was significantly higher among patients with HER2-positive breast cancer and

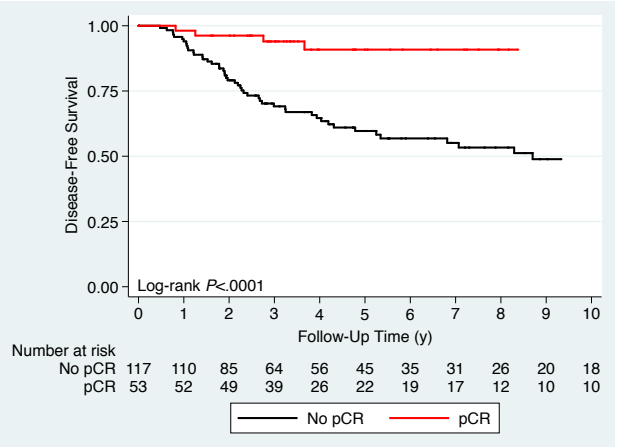


**Figure 1.** Disease-free survival among women aged ≤40 years who received neoadjuvant chemotherapy related to pathologic complete response (pCR).

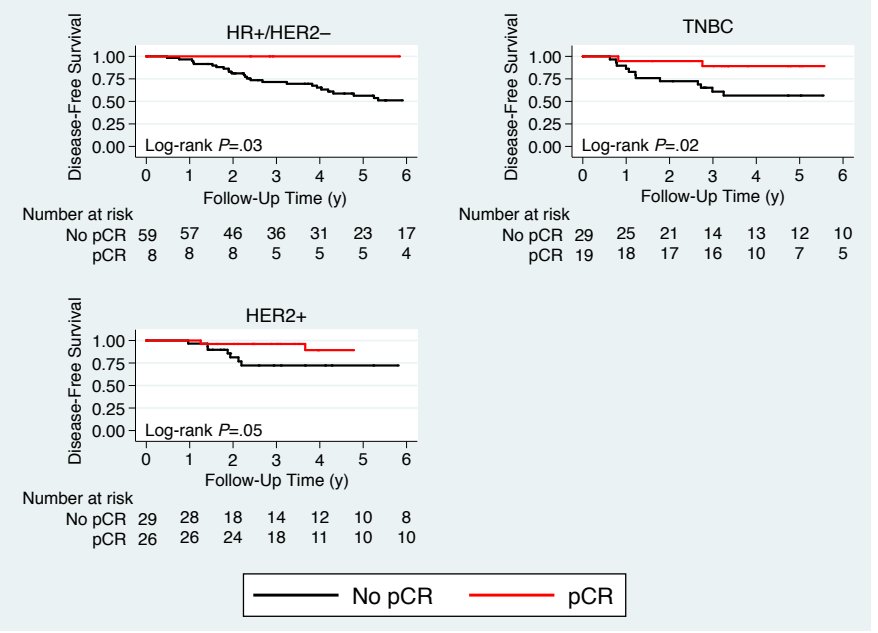


**Figure 2.** Disease-free survival by subtype based on pCR status.
Abbreviations: HR, hormone receptor; pCR, pathologic complete response; TNBC, triple-negative breast cancer.

TNBC compared with those with HR-positive/HER2-negative breast cancer, and higher rates of pCR were seen among patients with grade 3 tumors. The association of these clinicopathologic features with the occurrence of pCR in patients with breast cancer overall has been well described in several studies.[18–21] Improved DFS with pCR was seen regardless of disease subtype, including for HR-positive/HER2-negative breast cancer. In terms of baseline clinical stage, higher stage was only associated with worse long-term outcomes among patients with residual disease at the time of surgery in our analysis, further suggesting that pCR is a strong predictor of outcomes.

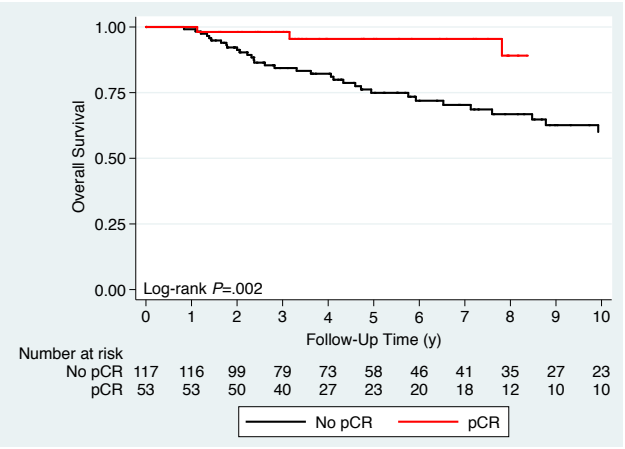


**Figure 3.** Overall survival among women aged ≤40 years who received neoadjuvant chemotherapy related to pathologic complete response (pCR).

We observed high rates of recurrence (29.4%) and mortality (22.9%) in the study population overall, largely due to patients who did not attain pCR. In a study by Partridge et al[4] using the NCCN Outcomes Database, among 1,875 women diagnosed at age ≤40 years with stage I–III breast cancer, there were 241 deaths (12.9% mortality rate) over a median follow-up period of 6.42 years. Our study represented a higher-risk subset of young women, given that all were stage II or III and received NAC. Additionally, the subtypes based on receptor status observed in our study are likely a skewed subset of the overall tumor types seen in young women, given that this is a subset selected for NAC.[22] Among the 3 disease recurrences in the pCR group, all were distant: 1 occurred in a patient with clinical stage IIB TNBC who underwent BCS, 1 in a patient with clinical stage IIIC HR-negative/HER2-positive disease who underwent mastectomy, and 1 in a patient with clinical stage IIB HR-negative/HER2-positive who underwent mastectomy. All 3 patients received standard of care neoadjuvant regimens and adjuvant radiation, and both patients with HER2-positive disease received adjuvant trastuzumab. Loibl et al[16] found the pCR rate to be signifi-

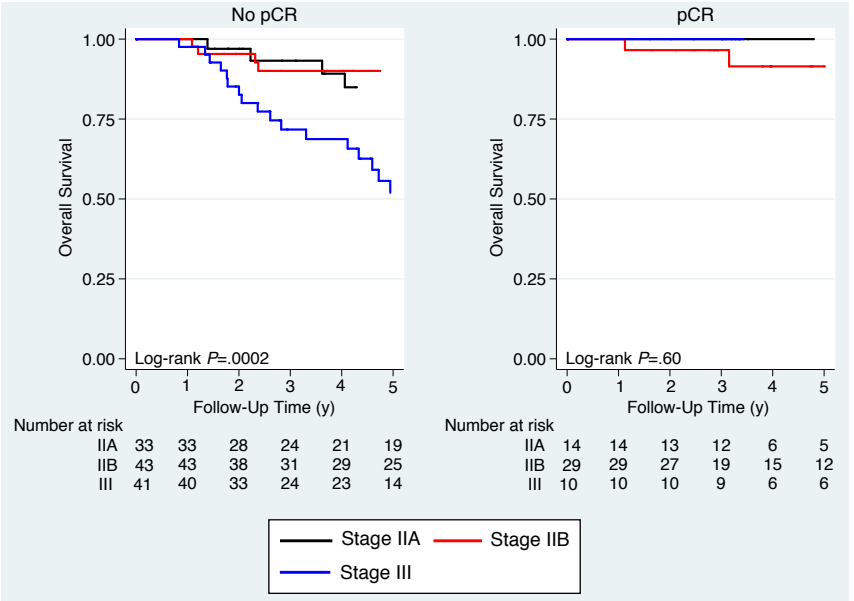


**Figure 4.** Overall survival by clinical stage based on pathologic complete response (pCR) status.

cantly higher in women <40 years of age compared with those aged 40 to 49 and ≥50 years (20.9% vs 17.7% vs 13.7%; *P*<.001), but recurrence and survival were significantly worse for young women. This suggests that young patients who do not have pCR after NAC may have worse outcomes compared with their older counterparts, which might be due to aggressive tumor biology and lower efficacy of adjuvant therapy, including endocrine therapy for HR-positive breast cancer in young women. For example, among patients with HR-positive disease, there are data in a Korean population suggesting very young women (age <35 years) are less likely to benefit from adjuvant hormone therapy, perhaps due to de novo tamoxifen resistance, highlighting the need to develop better therapies for this population.[6] Based on the results of the TEXT and SOFT trials, more high-risk young women are being treated with ovarian suppression and aromatase inhibitor therapy, which may help improve long-term outcomes for this population moving forward.[23–25] In the present study, only approximately 40% of patients underwent either surgical or medical ovarian suppression, given that clinical practice changed during the study period.

Attainment of pCR was associated with significantly reduced recurrence and improved survival regardless of baseline clinical stage in our study. This finding has implications for the neoadjuvant trial design and the development of individualized treatment based on the response to primary systemic therapy. The neoadjuvant setting has become recognized as an efficient model for drug development and is recognized by the FDA.[11,17,26] Given the potential toxicity associated with chemotherapy, particularly in young women with long life expectancies, novel trial designs featuring de-escalation of therapy after pCR are of interest. Conversely, consideration of salvage therapy when pCR is not attained is being explored. For example, CREATE-X, a multicenter, open-label, randomized phase III trial, evaluated capecitabine in patients with HER2-negative disease without pCR after anthracycline- and/or taxane-containing NAC.[27] The 2-year DFS rate was 87.3% for the capecitabine arm versus 80.5% for the control arm (hazard ratio, 0.69; log-rank *P*=.001), and the 2-year OS rate was 96.2% versus 93.9%, respectively (hazard ratio, 0.66; log-rank *P*=.09). Additional trials are investigating the role of platinum agents (ClinicalTrials.gov identifier: NCT02445391), as well as targeted therapies such as CDK 4/6 inhibitors (NCT01864746; PENELOPE-B), in patients with residual disease after NAC.

In our patient cohort, patients with pathogenic germline mutations had a higher rate of pCR overall. Approximately 16% of patients did not have germline genetic testing; some declined testing and

some who were diagnosed earlier in the study were not offered testing. Based on current guidelines, all patients in this age group should be offered testing. Most patients with pathogenic germline mutations had deleterious *BRCA1* mutations, which have been shown to be independently associated with higher pCR rates.[28] A retrospective study by Arun et al[28] demonstrated that *BRCA1* carriers who achieved a pCR had improved 5-year relapse-free survival compared with *BRCA1* carriers without pCR.[28] In general, *BRCA1*-associated breast cancer is more likely to be high-grade and poorly differentiated, and less likely to be HR-positive, which could account for the higher rates of pCR seen in this population.[29,30] Although the sample size was small, high rates of pCR were also seen among patients with germline *BRCA2*, *p53*, and *CHEK2* mutations in our study. Further research is needed, particularly among those with more rare mutations, to better understand the rates of pCR and associated prognostic significance, including the role of platinums and poly(ADP-ribose) polymerase (PARP) inhibitors. Several ongoing studies are anticipated to provide additional insight regarding the use of platinum and PARP inhibitors for *BRCA*-mutant breast cancer. For example, the INFORM study (ClinicalTrials.gov identifier: NCT01670500) is a randomized phase II trial of neoadjuvant cisplatin versus doxorubicin/cyclophosphamide in women with newly diagnosed breast cancer and germline *BRCA* mutations, and the OlympiA trial (NSABP B-55) is studying adjuvant use of the PARP inhibitor olaparib in patients with *BRCA*-mutant breast cancer (NCT02032823).

The present study has several limitations. It is a retrospective study representing the experience of a single, large academic institution, and comparisons with women aged >40 years were not made. Interaction terms were not used in the statistical analyses due to sample size, and likewise results need to be further confirmed in larger studies. Although treatment was taken into account, differential response to treatment and treatment heterogeneity in general could influence results.

Adjuvant treatment regimens may also influence recurrence rate and were not evaluated in our study. For example, 4 patients in our study did not receive adjuvant trastuzumab (due to evolving guidelines and patient preference), with 1 experiencing recurrence (pCR not achieved). Similarly, 7 HR-positive patients declined adjuvant endocrine therapy, with 4 experiencing disease recurrence. Also, selection bias for a higher-risk population is possible given that treatment was issued at a large academic medical center. The follow-up time in this study is also somewhat short for HR-positive breast cancer, and further analysis after longer follow-up is needed. Guidelines regarding receptor testing, particularly HER2, also evolved over the course of the study period. It is likely that some of the patients with HR-positive breast cancer who experienced pCR had low expression of ER and/or PR, suggesting biology more akin to TNBC. Breast cancer in the studied age group is also relatively rare, and therefore some analyses of interest, such as the role of platinum for TNBC in this population, are underpowered due to sample size.

## Conclusions

Attainment of pCR after NAC appears to be a robust surrogate marker for survival in young women with breast cancer. The high mortality rate of 22.9% in the study population overall largely reflects patients who did not attain pCR and highlights the need for better therapies for young women with breast cancer. Our results support the neoadjuvant trial design as an efficient method for rapid development and triage of novel and precision therapies for young women with breast cancer.

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