Published in final edited form as:

Breast Cancer Res Treat. 2010 December ; 124(3): 723–732. doi:10.1007/s10549-010-1181-8.

Preoperative concurrent paclitaxel-radiation in locally advanced breast cancer: pathologic response correlates with five-year overall survival

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Conflicts of interest A.B.C received research funding from Bristol-Meyers Squibb.

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Abstract

We have previously demonstrated high pathologic response rates after neoadjuvant concurrent chemoradiation in patients with locally advanced breast cancer (LABC). We now report disease-free survival (DFS) and overall survival (OS) in the context of pathologic response. 105 LABC patients (White 46%, Non-White 54%) were treated with paclitaxel (30 mg/m² intravenously twice a week) for 10–12 weeks. Daily radiotherapy was delivered to breast, axillary, and supraclavicular lymph nodes during weeks 2–7 of paclitaxel treatment, at 1.8 Gy per fraction to a total dose of 45 Gy with a tumor boost of 14 Gy at 2 Gy/fraction. Pathological complete response (pCR) was defined as the absence of invasive cancer in breast and lymph nodes and pathological partial response (pPR) as the persistence of <10 microscopic foci of invasive carcinoma in breast or lymph nodes. Pathologic response (pCR and pPR) after neoadjuvant chemoradiation was achieved in 36/105 patients (34%) and was associated with significantly better DFS and OS. Pathological responders had a lower risk of recurrence or death (HR = 0.35, $P = 0.01$) and a longer OS (HR = 4.27, $P = 0.01$) compared with non-responders. Median DFS and OS were 57 and 84 months for non-responders, respectively, and have not yet been reached for responders. Importantly, pathologic response was achieved in 54% of patients with HR negative tumors (26/48). In conclusion, pathologic response to concurrent paclitaxel-radiation translated into superior DFS and OS. Half of the patients with HR negative tumors achieved a pathologic response.

Keywords

Concurrent chemoradiation; Neoadjuvant; Locally advanced breast cancer; Survival; Pathologic response

Introduction

Neoadjuvant chemotherapy for breast cancer was introduced for women with locally advanced disease to render inoperable tumors resectable, and later extended toward enhancing the likelihood of breast conservation. In addition to providing information about tumor sensitivity to cytotoxic agents in vivo, pathologic response (pCR) to systemic therapies has demonstrated to be an invaluable intermediate endpoint, since it is a surrogate of DFS and OS after neoadjuvant therapy [1]. Patients achieving a pCR following anthracycline-based neoadjuvant chemotherapy achieve significantly superior DFS and OS compared with non-responders in large randomized trials such as the NSABP B-18 and B-27 [2]. However, with the exception of the subset of patients with tumors over-expressing human epidermal growth factor receptor-2 (Her2), that have high pCR rates when treated with regimens including trastuzumab [3–6], pCR rates following standard multi-agent chemotherapy remain relatively low, ranging from 7 to 31% [2, 7–17]. Pre-operative radiotherapy after neoadjuvant, anthracycline-based chemotherapy failed to significantly enhance the rate of pCR [18].

While superior outcomes after concurrent versus sequential chemotherapy and radiation (RT) have been demonstrated in other tumor types [19–23] with better local control and improved survival, studies of concurrent regimens are uncommon in breast cancer.

A prospective clinical trial of twice a week paclitaxel and concurrent radiotherapy in the neoadjuvant setting of LABC was conducted at three academic institutions, New York University (NYU), University of Southern California (USC), and Vanderbilt University School of Medicine: a consistent and encouraging pathologic response rate of 34% has been previously reported [24–26]. The current report focuses on the 5-year results of the 105 patients accrued to the trial, and analyzes outcomes in the context of pathologic response and original tumor characteristics.

Methods

Patients and procedures

Women 18 years of age with biopsy-proven LABC (stages IIB–IIIC), Eastern Cooperative Oncology Group performance status of 0 to 1, adequate bone marrow and organ function were eligible. Prior publications provide additional details on patient entry criteria, acute toxicity, and pathological response [24, 25]. Specifically, informed consent was obtained from all the patients in accordance with guidelines of the institutional review board of each institution. Tumor measurements were obtained by physical exam, mammography, and/or ultrasound at study entry. To guide the surgeon during the operation and facilitate evaluation for residual disease by the pathologist, the location of the tumor bed before neoadjuvant treatment was marked by tattoos (two largest perpendicular tumor diameters on the frontal plane). All the patients underwent further staging by computed tomographic (CT) scans of chest, abdomen, and pelvis, as well as bone scans to exclude detectable distant metastases.

Pathology

Standard immunohistochemistry was performed on the diagnostic core biopsy to determine estrogen receptor (ER) and progesterone receptor (PR) status on paraffin-embedded tissues. Staining in 10% of tumor cells was considered a positive result. ER+/PR+, ER+/PR–, and ER–/PR+ breast cancer were grouped as hormone receptor (HR) positive disease; ER–/PR– constituted the HR negative group. In more recent patients (85/105 patients), Her2 status was evaluated on paraffin-embedded tissue by immunohistochemistry; positivity was defined as 3+ over-expression or by fluorescence in situ hybridization (FISH), where positivity was defined as gene amplification (Her2 gene copy/chromosome 17 ratio 2.2).

Preoperative treatment

Primary therapy consisted of 30 mg/m² paclitaxel administered as a 1-h intravenous infusion twice weekly for a total of 10–12 weeks (Fig. 1). Pre-medication with dexamethasone, diphenhydramine, and H2 blockade was administered at the discretion of the treating physician. External-beam RT was initiated within 1 week of the first paclitaxel dose; daily radiotherapy was delivered to the breast, axillary, and supraclavicular lymph nodes during weeks 2–7, at 1.8 Gy per fraction to a total dose of 45 Gy followed by a boost of 14 Gy at 2 Gy per fraction to the originally palpable tumor. No deliberate attempt was made to encompass internal mammary nodes within the treated volume. After the FDA approval of this agent, patients enrolled after 2006 who had HER-2 positive tumors, received weekly trastuzumab (2 mg/kg) during the paclitaxel treatment (eight patients). Thirty-six patients at Vanderbilt University received three cycles of paclitaxel monotherapy (175 mg/m² every 3 weeks) prior to concurrent paclitaxel/RT. Their results were analyzed separately and in combination with the remaining patients.

Surgery

Patients underwent definitive breast cancer surgery approximately 4 weeks after completion of preoperative therapy or upon recovery of chemoradiation-induced dermatitis. Level I/II

axillary lymph node dissection was required for all the patients. The type of surgery (breast conserving vs. mastectomy) was decided by the surgeon.

Adjuvant treatment

Postoperatively, combination chemotherapy was recommended for all the patients regardless of pathologic response, as well as a minimum of 5 years of endocrine therapy for patients with HR positive cancer.

Pathologic response

Response was assessed in the surgical specimen obtained at definitive cancer surgery. Pathologic complete response (pCR) was defined as the absence of invasive cancer in breast and axillary lymph nodes (persistent ductal carcinoma in situ (DCIS) was allowed). Pathologic partial response (pPR) was defined as persistence of less than 10 microscopic foci of invasive tumor cells in breast and/or axillary contents. All the other patients were classified as having achieved no pathologic response (pNR).

Statistical analysis

The distribution of patient characteristics at entry was compared across the three institutions. Frequency distributions (for qualitative variables, e.g., stage, hormone receptor status) were compared using contingency table methods (chi-square and Fisher's exact tests). Age distributions were compared using analysis of variance methods. Response rates (pCR + pPR) were compared for the three institutions as well as by baseline characteristics using chi-square tests.

Overall survival was defined as time from definitive breast cancer surgery until death from any cause, with living patients censored at date of last contact. Disease-free survival was defined as time from definitive breast cancer surgery to first recurrence of breast cancer, or death from any cause. OS and DFS were summarized using Kaplan–Meier methods. Point estimates and 95% confidence intervals for 5-year OS and DFS are reported. Log-rank methods and Cox proportional hazards models were used to examine the effects of pathologic response and baseline disease characteristics individually and jointly on DFS and OS. Univariate and multivariable Cox proportional hazards models were developed to predict OS and DFS based on patient and disease characteristics using stepwise regression procedures. Final models were selected using SAS stepwise procedures and likelihood ratio tests. Hazard ratios and 95% confidence intervals are reported. All the statistical tests are two-sided.

Results

105 patients were treated with concurrent preoperative paclitaxel-radiation between March 1997 and August 2009; 33 at USC, 36 at NYU, and 36 at Vanderbilt University.

Patient baseline characteristics are reported by institution in Table 1. With the exception of differences in the distributions of race and stage, all characteristics are similar across the three institutions.

Pathologic response

Pathologic response (pCR and pPR) after preoperative chemoradiation was achieved in 36/105 patients (34%, 95% confidence interval: 25–44%). Response rates were similar across the three institutions, including the cohort at one institution that received three cycles of paclitaxel monotherapy prior to concurrent chemoradiation (Table 1).

The pathologic response rate was significantly higher in patients with HR negative tumors (26/48 patients, 54%, 95% CI 39–69%) than in patients with HR positive tumors (10/57 patients, 18%, 95% CI 9–30%, $P < 0.0001$).

Among the 85 patients for whom Her2 status is available, a pathologic response was achieved in 6/34 patients with HR+/Her2– tumors (17.6%), 3/13 patients with HR+/Her2+ tumors (23.1%), 13/24 patients with HR–/Her2– (triple negative) tumors (54.2%). Pathological response occurred in 7/14 patients with HR–/Her2+ cancers (50%), with 3/7 having received trastuzumab. Of the patients for whom Her2 status was not available, 60% (6/10) of HR negative patients had a pathologic response compared to 10% (1/10) of HR positive patients (2-sided Fisher's exact test, $P = 0.06$). Table 2 describes the pathological response rate for breast cancer subtypes, based on HR and Her2 status and trastuzumab therapy.

Recurrences and second primary breast cancers

Recurrences manifested themselves mainly as distant metastases. Distant metastases were observed in 24/105 patients (22.9%): 6/36 patients with a pathologic response recurred (13%) compared with 23/69 non-responders (33%). Five-year loco-regional control was achieved in 95.2% of patients. Five patients experienced a local recurrence, one being an isolated event and the remaining four occurring synchronously with or following systemic recurrence. Invasive new contralateral breast cancers occurred in five patients (4.8%).

Disease-free and overall survival

At a median follow-up of 60 months, the median DFS and OS have not been reached. The estimated 5-year DFS is 61.4% (95% CI: 50.1–70.8%), the 5-year OS is 71.6% (95% CI: 60.5–80.1%) (Fig. 2).

Association of pathologic response with disease-free and overall survival

Pathologic response was associated with an improved long-term outcome, regardless of HR status (Fig. 3). Patients with a pathologic response had a significantly longer DFS than patients without a pathologic response (hazard ratio = 2.85, 95% CI: 1.25–6.51, log-rank P -value = 0.01) (Fig. 3a, b). Similarly, responders had a longer OS (4.27 times greater) over the time period than non-responders (95% CI: 1.48, 12.29) (Fig. 3c, d).

The median DFS was 57 months for non-responders and has not yet been reached for responders. The median OS was 84 months for non-responders and has not yet been reached for patients achieving a pathological response.

Among all variables tested (listed in Table 3), pathologic response was the only predictor of OS. HR negative patients achieving a pathologic response had a comparable OS to that of the HR positive responders (Fig. 3d).

We note that when institution is included in these models, there is no effect on DFS or OS.

Discussion

To our knowledge, this is the first report of the effect of pathological response to neoadjuvant concurrent chemoradiation on DFS and OS for LABC patients treated in a prospective clinical trial. With a median follow-up of 60 months, the estimated 5-year OS for the entire cohort treated with neoadjuvant paclitaxel/RT is 71.6%, a result comparable to that achieved in LABC patients treated by neoadjuvant chemotherapy, followed by surgery and adjuvant radiotherapy [10, 12, 27–34].

Of 105 patients treated with neoadjuvant paclitaxel/RT, 36 (34%) achieved a pathologic response. This response rate was consistently achieved at each of the three academic centers. The criteria for assessment of pathological response used in this series were originally defined in the mid-1990s, at USC [26]. Currently, there are more than eight proposed classifications for pathological response [11, 35–40]. To standardize response definitions, the Breast Cancer Task Force included a post-neoadjuvant therapy staging category in the revised American Joint Committee on Cancer (yAJCC) staging system for breast cancer [41]. Complete response is defined as the absence of invasive tumor in breast and lymph nodes (yAJCC stage 0), consistent with our definition of pCR [35, 38]. However, in contrast to some other studies, we combined pCR and pPR as pathologic response, therefore including patients with less than 10 microscopic foci of invasive cancer in our cohort of responders. The rationale for this criterion is based on the short duration of the concurrent chemoradiation approach (less than 2 months for most patients), possibly a period of time insufficient to enable complete clearance of tumor cells, hence the inclusion of pPR. Others have reported residual minimal invasive disease in the breast (Residual Breast Cancer Burden (RCB)-1) as prognostically similar to cases with absent invasive disease (RCB-0) [38]. Noticeably, when clinical outcomes were analyzed separately for pCR and pPR in our series, there were no differences in OS or DFS between these two groups (Log-rank Test, data not shown).

The median follow-up for the study cohort is 60 months. For the entire cohort, achievement of a pathologic response was associated with significantly fewer breast cancer recurrences and deaths at 5-year analysis. To our knowledge, this is the first prospective study that reports an association of pathologic response with survival after primary concurrent chemoradiation. The results reported are comparable to those from a large retrospective cohort of 1,117 LABC patients treated with concurrent chemoradiation in South India: pathologic response occurred in 33% of patients and was associated with improved DFS, consistent with our findings [42].

In the current series, the pathologic response rate of 54% in patients with triple-negative breast cancer compares favorably to the results achieved by neoadjuvant chemotherapy [43–45]: the fact that HR negative cancer carriers who achieved a pathological response had a similar OS as HR positive responders warrants further exploration in this subset of breast cancer patients.

This finding that a single agent regimen, like the one tested, when given with concurrent radiotherapy could achieve a pathological response prognostically similar to that achieved by standard neoadjuvant poly-chemotherapy is noteworthy. Several hypotheses can explain these results. First of all, it is possible that in tumors more sensitive to taxanes and radiation, the concurrent administration of the two modalities successfully eliminated the subset of cancer cells later destined to become circulating cells with seeding potential [46] and/or eradicated CD44⁺/CD24^{low} or aldehyde dehydrogenase 1 (ALDH1)⁺ tumor cells, shown to possess tumor-initiating potential if they persist after treatment [47, 48]. In a study conducted on tumor specimens of the patients in this cohort who had adequate pre- and posttreatment biopsies, we reported the association of pathological response with over-expression of MAP2 at micro-array analysis [49], a possible explanation of enhanced sensitivity to taxanes [50].

A novel hypothesis for the systemic benefit of concurrent chemoradiation is the effective induction of protective anti-tumor immunity. In the study mentioned above, we also found an association of pathological response with distinct immune signatures [49]. At proteomic analysis a-defensins (DEFA) [51] expression was associated with increased immune infiltrates, and significantly correlated with pCR, particularly among triple-negative patients

(58%). These findings were confirmed at genomic analysis and are consistent with those reported by Kreike et al. [52] who demonstrated that clusters of interferon-regulated and immunoglobulin genes were >3-fold increased in triple-negative tumors who achieved a pathological response. In addition to their cytotoxic effects standard anti-cancer modalities such as certain chemotherapy agents and radiotherapy can generate an immunogenic cell death, converting the original tumor into an in situ immunogenic hub [53–57]. In preclinical models, the acquired anti-tumor immune response contributes to tumor pathological responses that can also control micro-metastatic foci [54].

Finally, half of the patients in this series were Non-Caucasian women (54%), and the majority of women were treated at a public hospital. When analyzed, ethnicity did not have an impact on the achievement of pathologic response or outcomes. The population with LABC in the US often consists of minority and underserved women, more likely to experience challenges to adherence because of cultural and language barriers, resident status, lack of medical insurance, etc. It is therefore not surprising that 12 patients (11% of study population) were lost to follow-up despite intense efforts by the multidisciplinary team and patient navigators.

In summary, in spite of adverse characteristics in our patient population, our data suggest that preoperatively administered concurrent paclitaxel/radiation achieves comparable results to those of modern neoadjuvant chemotherapy with respect to pathologic response rate and OS. Most importantly, patients with HR negative tumors had a 54% chance of achieving a pathologic response, which translated into improved DFS and OS. Since paclitaxel is available in its generic form and the radiotherapy regimen of this trial is comparable to that currently used in standard regimens of neoadjuvant poly-chemotherapy followed by surgery and postoperative radiation, the comparative effectiveness of this approach warrants further study. However, only a prospective randomized study comparing concurrent chemo-radiation to the sequential standard protocol can establish the role of this approach.

Acknowledgments

We thank all the participating patients, treating physicians, and research teams at NYU, USC, and Vanderbilt University. The study was supported by the: Department of Defense Breast Cancer Research Program Center of Excellence (W81XWH-04-1-0905, to S.C.F., J.D.G., T.H. and R.J.S.), American Cancer Society (TURSG CCE 103174, to S.C.F.), National Institutes of Health Grants 5P30 CA016037-30 (NYU Core Services), K23CA125205P50 (to S.A.), CA95131 (Specialized Program of Research Excellence in Breast Cancer, to J.A.P.); CA105436 and CA070856 (to J.A.P.); ES00267 and CA68485 (Vanderbilt Core Services); CA009385 and CA138106 (to J.A.B.); US Army grant DAMD17-99-1-9422 (to J.A.P.); California Breast Cancer Research Program BCRP TRC 4E-6000 (to S.C.F.), Breast Cancer Research Foundation (to S.C.F. and R.J.S.), Avon Foundation 15D1500-36300 (to S.C.F. and R.J.S.), New York University General Clinical Research Center (NIH/NCRR M01 RR000096), and a Vanderbilt-Ingram Cancer Center Discovery Grant (to A.B.C.).

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Fig. 1.
Treatment schema

Fig. 2.
Overall survival and disease-free survival for the entire cohort

Fig. 3. Kaplan Meier estimates of overall survival and disease-free survival **a** DFS by pathologic response for entire cohort, **b** DFS by pathologic response and HR status, **c** OS by pathologic response for entire cohort, and **d** OS by pathologic response and HR status. *HR* hormone receptor, *pCR* pathologic complete response, *pPR* pathologic partial response, *pNR* no pathologic response

Table 1

Baseline characteristics and pathologic response rates for the entire cohort (105 patients) and by institution

Patient characteristics	NYU (N = 36)	USC (N = 33)	Vanderbilt (N = 36)	Total (N = 105)	All group P-value
Race					
Caucasian	13 (36%)	5 (15%)	30 (83%)	48 (46%)	<0.001 ^{a, A}
Non-Caucasian	23 (64%)	28 (85%)	6 (17%)	57 (54%)	
Hispanic	7 (19%)	21 (64%)	0	28 (27%)	
African American	7 (19%)	1 (3%)	5 (14%)	13 (12%)	
Asian	9 (25%)	6 (18%)	1 (3%)	16 (15%)	
Age	Mean = 50.0 SD = 11.06	Mean = 48.5 SD = 12.3 S	Mean = 47.4 D = 11.4	Mean = 48.6 SD = 11.5	0.64 ^c
Age ≤ 50	20 (56%)	21 (64%)	20 (56%)	61 (58%)	0.74 ^a
Age > 50	16 (44%)	12 (36%)	16 (44%)	44 (42%)	
AJCC Stage					
II	19 (53%)	10 (31%)	22 (61%)	51 (49%)	0.04 ^a
III	17 (47%)	22 (69%)	14 (39%)	53 (51%)	
Missing		1		1	
Tumor Grade					
I	1 (3%)	0	4 (11%)	5 (7%)	0.44 ^b
II	14 (41%)	0	14 (39%)	28 (38%)	
III	19 (56%)	3 (100%)	18 (50%)	40 (55%)	
Missing ^d	2	30		32	
ER					
Negative	12 (33%)	19 (58%)	19 (53%)	50 (48%)	0.10 ^a
Positive	24 (67%)	14 (42%)	17 (47%)	55 (52%)	
PR					
Negative	22 (61%)	20 (61%)	22 (61%)	64 (61%)	1.00 ^a
Positive	14 (39%)	13 (39%)	14 (39%)	41 (39%)	
HR status					
Negative	12 (33%)	17 (52%)	19 (53%)	48 (46%)	0.18 ^{a, ^^}
Positive	24 (67%)	16 (48%)	17 (47%)	57 (54%)	
ER+PR–	10 (28%)	3 (9%)	3 (8%)	16 (15%)	
ER+PR+	14 (39%)	11 (33%)	14 (39%)	39 (37%)	
ER–PR+	0	2 (6%)	0	2 (2%)	
Her2 status					
Negative	26 (72%)	11 (79%)	21 (60%)	58 (68%)	0.36 ^a
Positive	10 (28%)	3 (21%)	14 (40%)	27 (32%)	
Missing		19	1	20	
Pathologic response					
pCR/pPR	11 (31%)	10 (30%)	15 (42%)	36 (34%)	0.52 ^a

Patient characteristics	NYU (N = 36)	USC (N = 33)	Vanderbilt (N = 36)	Total (N = 105)	All group P-value
<i>pCR</i>	8 (22%)	5 (15%)	11 (31%)	24 (23%)	
<i>pPR</i>	3 (8%)	5 (15%)	4 (11%)	12 (11%)	
<i>pNR</i>	25 (69%)	23 (70%)	21 (58%)	69 (66%)	

NYU New York University, USC University of Southern California, *N* number, *SD* standard deviation, *AJCC* American Joint Commission on Cancer, *ER* estrogen receptor, *PR* progesterone receptor, *Her2* human epidermal growth factor receptor, *pCR* pathologic complete response, *pPR* pathologic partial response, *pNR* no pathologic response

[^] *P*-values based on Caucasian vs. non Caucasian

^{^^} *P*-value base on positive versus negative

^a Chi-square test

^b Fisher exact test

^c F-Statistic

^d Only nuclear grade was reported

Table 2

Pathologic response rate for breast cancer subtypes based on HR and Her2 status

Subtype	Total	Proportion of patients who received trastuzumab	Proportion of patients with pathologic response (pCR + pPR)
Entire cohort ($n = 105$)			
HR positive	57	5/57 (2 with pathologic response)	10/57 (18%)
HR negative	48	3/48 (3 with pathologic response)	26/48 (54%)
Cohort with Her2 status available ($n = 85$)			
HR positive/Her2 negative	34	N/A	6/34 (17.7%)
HR positive/Her2 positive	13	5/13 (2 with pathologic response)	3/13 (23.1%)
HR negative/Her2 positive	14	3/14 (3 with pathologic response)	7/14 (50.0%)
HR negative/Her2 negative (triple negative)	24	N/A	13/24 (54.2%)

HR hormone receptor, *Her2* human epidermal growth factor receptor, *pCR* pathologic complete response, *pPR* pathologic partial response

Table 3

Hazard ratios for disease-free survival and overall survival by baseline characteristics (Cox proportional hazards models)

Patient characteristics	Disease-free survival				Overall survival	
	Univariate analysis		Multivariable analysis		Univariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Race						
Asian vs. Caucasian	1.49 (0.51–4.39)	0.47			1.62 (0.47–5.56)	0.45
Black vs. Caucasian	1.24 (0.42–3.64)	0.69			0.92 (0.31–2.75)	0.88
Hispanic vs. Caucasian	1.27 (0.57–2.80)	0.56			2.06 (0.75–5.68)	0.16
Age	1.004 (0.98–1.03)	0.78			1.00 (0.97–1.03)	0.99
AJCC Stage						
II vs. III	2.01 (1.02–3.94)	0.04			1.98 (0.92–4.25)	0.08
Tumor grade						
I/II vs. III	1.12 (0.55–2.27)	0.76			0.99 (0.45–2.19)	0.57
ER						
Positive vs. Negative	1.29 (0.68–2.47)	0.44			0.83 (0.40–1.73)	0.62
PR						
Positive vs. Negative	1.41 (0.72–2.77)	0.32			1.05 (0.50–2.20)	0.91
HR status						
Positive vs. Negative	1.30 (0.68–2.47)	0.43	2.18 (1.10–4.33)	0.03	0.80 (0.38–1.69)	0.56
Her2 status						
Positive vs. Negative	0.67 (0.32–1.43)	0.3			0.63 (0.27–1.49)	0.29
Pathologic response						
pCR/pPR vs. pNR	2.85 (1.25–6.51)	0.01	4.08 (1.70–9.80)	0.002	4.27 (1.48–12.29) ^a	0.01

^aBest fit model chosen from stepwise selection procedures based on likelihood ratio criterion; only pathologic response influences survival when additional variables are included in overall survival models

HR hazard ratio, CI confidence interval, AJCC American Joint Commission on Cancer, ER estrogen receptor, PR progesterone receptor, HR hormone receptor, Her2 human epidermal growth factor receptor, pCR pathologic complete response, pPR pathologic partial response, pNR no pathologic response