


RESEARCH PAPER



The treatment option of progressive disease in breast cancer during neoadjuvant chemotherapy: a single-center experience

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ABSTRACT

Patients' responses to breast cancer neoadjuvant chemotherapy (NACT) differ because of heterogeneous tumor characteristics. Reports about NACT progression are sporadic. Here we enrolled 1187 patients who received NACT in our cancer center between January 1, 2007, and December 31, 2016. We analyzed the characteristics and treatments of patients with progressive disease (PD) or non-PD or pathological complete response (pCR). In total, 45 (3.8%) patients had PD. PD patients were associated with a significantly worse disease-free survival (DFS) (hazard ratio (HR) = 3.77; 95% CI, 1.77 to 8.00; $P = .001$) and overall survival (OS) (HR = 3.85; 95% CI, 1.77 to 8.35; $P = .001$). For the PD patients, 28 (62.2%) patients received mastectomy immediately after PD, and 17 (37.8%) changed to chemotherapy. DFS and OS exhibited no significant differences between these two salvage therapies. After a change to second chemotherapy, 58.8% (10/17) patients had PD or SD. With the exception of tumor size, pretreatment T stage, and histology type, no other significant differences were noted between PD and pCR patients. Our results demonstrated that PD patients were associated with a significantly worse prognosis. Based on these results, we suggest to give the addition of trastuzumab to HER-2 positive patients instead of changing the chemotherapy regimen and proceeding to surgery instead of further chemotherapy once patients have PD during NACT. Given that some similar characteristics exist between PD and pCR patients, more studies to identify novel molecular markers to predict disease response to NACT should be performed.

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Introduction

For larger operable breast cancers, an increasing number of patients undergo neoadjuvant chemotherapy (NACT).¹ In addition to improving breast-conservation surgery rates, NACT can make inoperable locally advanced breast cancer operable. Furthermore, NACT can be used as an *in vivo* test for chemosensitivity by assessing pathologic complete response (pCR), which correlates with longer overall survival (OS) and disease-free survival (DFS).^{2,3} However, a small number of patients exhibit minimal sensitivity to or even progress on NACT and thus will not benefit from months of treatment, which may make breast-conservation surgery or even mastectomy impossible.⁴

Numerous studies worldwide, including both in Western countries and Asia, have focused on NACT. However, even in Western countries, the reports about progressive disease (PD) are sporadic. To date, only 2 studies focused on PD.⁵⁻⁷ Much less is known about NACT in Asian patients, and reports on PD in Asian people are not available. The epidemiologic and clinical outcome data of breast cancer women in Asia differ from that in Western populations. Invasive breast cancer in Asia is 30% of that in Northern America and Europe.⁸ The peak age for breast cancer in Asia is between 40 and 50 years,

whereas the peak age is between 60 and 70 years in most Western countries.⁹ Other differences include race, environmental factors, genetic variation, socioeconomic status, and stage of disease at diagnosis.¹⁰ Given that most NACT strategies for breast cancer were established in the United States and Europe, the validity of NACT has been rarely evaluated in Asian patients.¹¹

Although the PD rate is low, the absolute number of PD cases tends to be high given the large population in China and other Asian countries. Consequently, even a small increase in PD may lead to a poor outcome in a large number of patients. Once a patient's tumor progresses during NACT, different salvage treatment approaches are used, such as surgery, salvage chemotherapy and radiation therapy.⁷ However, given the low incidence rate of PD, no standard therapy protocol is achieved. Therefore, it is desirable to gain more knowledge regarding the clinical and biological features of PD patients. Once a patient experiences PD, individualized treatment can be used based on tumor characteristics. In the present study, we evaluated Chinese PD patients' characteristics and treatments and discerned whether PD characteristics differed between Asian and Western countries. Thus, when PD occurs, we will have protocols available to maximize salvage treatments.

Methods

Study population

All of the patients included in this retrospective study were selected from patients with invasive breast cancer treated with NACT at the Zhejiang Cancer Hospital between January 1, 2007, and December 31, 2016. Patients were excluded who were male, had distant metastasis at the time of initial diagnosis, had inflammatory breast cancer, were treated synchronously for another primary cancer, underwent excisional biopsies of the primary breast tumor before the start of chemotherapy, or had bilateral primary breast cancer.

Response criteria

The assessment of tumor burden was based on the Revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)¹² based on the following definitions. Tumors and lymph nodes were scanned with ultrasound system prior to chemotherapy treatment, every two cycles of treatment or any point of time if necessary, and prior to surgery. PD is defined as at a minimum of a 20% increase in the sum of diameters of target lesions. Partial response (PR) is defined as a minimum of a 30% decrease in the sum of diameters of target lesions. Stable disease (SD) is defined as neither adequate decrease to qualify for PR nor sufficient increase to qualify for PD. Clinical complete response (cCR) is defined as disappearance of all target tumors by clinical evaluation. Pathologic complete response (pCR) is defined as the absence of an invasive tumor and in-situ cancer in the breast and axillary nodes by histopathologic evaluation.

Statistical analysis

The medical record was reviewed to obtain data on patient disease, treatment characteristics, and clinical outcomes using descriptive statistics. Continuous variables were reported as the means and medians with standard deviation, and minimum and maximum ranges were also reported. Categorical variables were reported as frequency counts and proportions. T test for continuous variables and Fisher's exact test or χ^2 test for categorical variables were used for comparisons between groups. OS was defined as the time from diagnosis to death. DFS was defined as the time from diagnosis to recurrence (local, regional or distant) or death, whichever occurred first. Patients without an event were censored at the date of last follow-up. OS and DFS for all the patients were estimated using the Kaplan–Meier method. Survival prognostic factors were examined using the log-rank test and Cox proportional hazards regression analysis. The probabilities of progression were examined by logistic regression. Both factors above were analyzed in univariate and multivariate fashion. A forward stepwise method was used to obtain the final model. A hazard ratio (HR) or odds ratio (OR) for each prognostic factor was determined with a 95% CI. $P < .05$ was considered to be statistically significant. Analyses were conducted using SPSS® version 23.

Results

Patient characteristics

A total of 1187 women patients who received NACT were enrolled in the study. Baseline patient characteristics in each group are listed in Table 1. Among these patients, 45 (3.8%) patients had PD, 142 (12.0%) patients had SD, 873 (73.5%) patients had PR and 127 (10.7%) patients had cCR. Patients with PD were compared with patients without PD (including SD, PR and cCR).

Median ages were 48 years (range, 21 to 65 years) for patients with PD and 49 years (range, 23 to 76 years) for patients without PD. Of the PD group 30 (67%) were premenopausal compared with 646 (57%) of the non-PD cases. There was no difference in body mass index (BMI) and family history of cancer between the two groups. In the PD group, 4 (8.9%) tumors were T1, 19 (42.2%) were T2, 13 (28.9%) were T3, and 9 (20.0%) were T4. In the non-PD group, there were 77 (6.7%), 760 (66.5%), 159 (13.9%) and 146 (12.8%) patients with T1, T2, T3 and T4 disease, respectively ($P = .006$). Although there was no difference in tumor size between groups (39.0 mm vs. 34.5 mm, $P = .133$), the PD groups had larger tumors compared with the non-PD group. Additionally, no significant difference was observed between the two groups regarding lymph node status and American Joint Committee on Cancer (AJCC) stage. However, patients in the PD group were more likely to have stage IIIA–IIIC disease compared with patients in the non-PD group (55.6% vs. 45.9%, respectively). Regarding pretreatment histopathologic characteristics, the median ki-67 score was 50 in the PD group, which was increased compared with the non-PD group (median score was 30, $P = .01$).

In terms of tumor subtypes, the PD group was more likely to have estrogen receptor (ER)-negative ($n = 31$, 68.9%) and progesterone receptor (PR)-negative tumors ($n = 32$, 71.1%) compared with the non-PD group (with $n = 465$, 41.5% in ER-, $P = .001$ and $n = 656$, 58.5% in PR-, $P = .016$). Human epidermal growth factor receptor 2 (HER-2) status did not differ between the two groups. Histology significantly differed between the two groups. In addition to ductal and lobular histology, PD tumors exhibited greater proportions of mixed (5, 11.1%) and other (4, 8.9%) types of histology, such as metaplastic carcinomas (MPCs), invasive micropapillary carcinoma, signet ring cell carcinoma, neuroendocrine carcinoma, and sarcoma (such as fibrous histiocytoma and liposarcoma). In the non-PD group, only 21 (1.8%) mixed types and 23 (2.0%) other types were observed. Although the nuclear grade was only determined in 372 (31.4%) patients, the PD group was more likely to present with grade 3 tumors ($n = 14$ (31.1%)) compared with the non-PD group ($n = 117$ (10.2%), $P < .001$).

Post-treatment pathologic results

The characteristics of tumors after chemotherapy also are presented in Table 1. Pathologic tumor size (median tumor size, 55.0 mm for PD and 20.0 mm for non-PD, $P < .001$), T stage ($P < .001$), N stage ($P = .003$) and AJCC stage ($P < .001$) all exhibited significant differences between the

Table 1. Pretreatment and post-treatment patient characteristics.

Characteristic	Pretreatment patient characteristics		P	Post-treatment patient characteristics		P
	PD (n = 45, 3.8%) No. of Patients (%)	non-PD (n = 1142, 96.2%) No. of Patients (%)		PD (n = 45, 3.8%) No. of Patients (%)	non-PD (n = 1142, 96.2%) No. of Patients (%)	
Age, years			.325			
Median	48 (-)	49 (-)		-	-	
Range	21–65	23–76		-	-	
Menopausal status			.180			
Premenopausal	30 (66.7)	646 (56.6)		-	-	
Postmenopausal	15 (33.3)	496 (43.4)		-	-	
Family history of cancer			.497			
Breast cancer	2 (4.4)	37 (3.2)		-	-	
Other cancers	6 (13.3)	226 (19.8)		-	-	
No	37 (82.2)	872 (76.4)		-	-	
Unknown	0 (0.0)	7 (0.6)		-	-	
BMI ^a			.411			
Median	23.2 (-)	23.5 (-)		-	-	
Range	14.9–30.8	15.6–34.9		-	-	
Ki-67 score ^b			.001			
Median	50.00 (-)	30.00 (-)		-	-	
Range	5–90	0–95		-	-	
ER status			.001			
Negative	31 (68.9)	465 (41.5)		-	-	
Positive	14 (31.1)	656 (58.5)		-	-	
Unknown	0 (0)	21 (1.8)		-	-	
PR status			.016			
Negative	32 (71.1)	568 (49.7)		-	-	
Positive	13 (28.9)	550 (48.2)		-	-	
Unknown	0 (0.0)	24 (2.1)		-	-	
Her-2 status			.884			
Negative	21 (46.7)	563 (49.3)		-	-	
Positive	16 (35.6)	416 (36.4)		-	-	
Uncertain	6 (13.3)	132 (11.6)		-	-	
Unknown	2 (4.4)	31 (2.7)		-	-	
Histology			.000			
Ductal	34 (75.6)	1074 (94.0)		-	-	
Lobular	2 (4.4)	14 (1.2)		-	-	
Mixed	5 (11.1)	21 (1.8)		-	-	
Other	4 (8.9)	23 (2.0)		-	-	
Unknown	0 (0.0)	10 (0.9)		-	-	
Nuclear grade			.000			
I	0 (0.0)	21 (1.8)		-	-	
II	4 (8.9)	217 (19.0)		-	-	
III	14 (31.1)	117 (10.2)		-	-	
Unknown	27 (60.0)	787 (68.9)		-	-	
Tumor size, mm			.133			<.001
Median	38.0 (-)	34.5 (-)		55.0	20.0	
Range	13.0–130.0	5.0–160.0		0–230	0–120	
T stage			.006			<.001
T0	-	-		1 (2.2)	176 (15.4)	
Tis	-	-		0 (0.0)	19 (1.7)	
T1	4 (8.9)	77 (6.7)		5 (11.1)	490 (42.9)	
T2	19 (42.2)	760 (66.5)		13 (28.9)	356 (31.2)	
T3	13 (28.9)	159 (13.9)		13 (28.9)	55 (4.8)	
T4	9 (20.0)	146 (12.8)		13 (28.9)	46 (4.0)	
N stage			.622			.003
N0	7 (15.6)	136 (11.9)		9 (20.0)	366 (32.0)	
N1	28 (62.2)	657 (57.5)		13 (28.9)	325 (28.5)	
N2	7 (15.6)	222 (19.4)		6 (13.3)	254 (22.2)	
N3	3 (6.7)	127 (11.1)		17 (37.8)	197 (17.3)	
AJCC stage			.237			<.001
0	-	-		1 (2.2)	132 (11.6)	
IA	0 (0.0)	1 (0.1)		1 (2.2)	153 (13.4)	
IIA	8 (17.8)	140 (12.3)		6 (13.3)	269 (23.6)	
IIB	12 (26.7)	476 (41.7)		8 (17.8)	117 (10.2)	
IIIA	14 (31.1)	272 (23.8)		6 (13.3)	245 (21.5)	
IIIB	8 (17.8)	128 (11.2)		6 (13.3)	30 (2.6)	
IIIC	3 (6.7)	125 (10.9)		14 (31.1)	196 (17.2)	
IV	-	-		3 (6.7)	0 (0.0)	
Lymphovascular invasion						.178
Positive	-	-		20 (44.4)	396 (34.7)	
Negative	-	-		25 (55.6)	746 (65.3)	
Chemotherapy regimen						
Anthracycline-based	-	-		37 (82.2)	1016 (89.0)	.161
Taxane-based	-	-		31 (68.9)	1040 (91.1)	.000
Trastuzumab	-	-		2 (4.4)	117 (10.2)	.309

(Continued)

Table 1. (Continued).

Characteristic	Pretreatment patient characteristics			Post-treatment patient characteristics		
	PD (n = 45, 3.8%)	non-PD (n = 1142, 96.2%)	P	PD (n = 45, 3.8%)	non-PD (n = 1142, 96.2%)	P
	No. of Patients (%)	No. of Patients (%)		No. of Patients (%)	No. of Patients (%)	
Surgery						.792
BCT	-	-		1 (2.2)	33 (2.9)	
Mastectomy	-	-		44 (97.8)	1109 (97.1)	

Abbreviations: PD, progressive disease; BMI, body mass index; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2; BCT, breast-conserving therapy.

^aBMI was available in 45 patients in the PD group and 1136 patients in the non-PD group.

^bKi-67 scores were available in 27 patients in the PD group and 712 patients in the non-PD group.

two groups. Compared with non-PD patients, PD patients were more likely to have T3-4, N2-3, and IIIA-IV stage tumors (57.8% vs. 8.8%, 51.1% vs. 39.5%, 64.5% vs. 41.3%, respectively). Although lymphovascular invasion did not differ between the two groups ($P = .178$), the condition was more prevalent in the PD group compared with the non-PD group with 20 (44.4%) cases in the PD group and 396 (34.7%) cases in the non-PD group. Chemotherapy regimens based on anthracycline and trastuzumab did not differ between the two groups ($P = .249$, and 1.000 respectively). Chemotherapy regimens based on taxane ($P < .001$) exhibited differences. In total, 1040 (91.1%) of non-PD patients received taxane-based chemotherapy, whereas only 31 (68.9%) of PD patients received taxane-based chemotherapy. Both PD patients and non-PD patients had similar breast-conserving therapy (BCT) and mastectomy rates. In total, 1 (2.2%) patient in the PD group and 33 (2.9%) patients in the non-PD group had BCT. In total, 44 (97.8%) patients in the PD group and 1109 (97.1%) patients in the non-PD group had a mastectomy.

PD patients' therapy

With regard to the treatments administered, 37(82.2%) patients had PD while receiving anthracycline-based therapy, and 31(68.9%) patients had PD while receiving taxane (T)-based therapy. Fourteen (31.1%) patients used a NACT regimen based on anthracycline during PD, and 23 (51.1%) patients used a NACT regimen based on anthracycline and cyclophosphamide(EC) during PD. Two (4.4%) patients used a NACT regimen based on taxane during PD. Five (11.1%) patients had SD during anthracycline and experienced PD after switching to taxane. One (2.2%) patient had SD during the EC regimen but experienced PD after changing to a vinorelbine and capecitabine regimen. Of the PD patients, 9 (20%) received EC-T regimen and of these 5 had SD during anthracycline and experienced PD after switching to taxane. Four patients experienced PD while taking an anthracycline regimen, and 3 patients experienced a second PD after switching to taxane. One patient experienced PR after switching to taxane. Sixteen (35.6%) PD patients exhibited HER-2 overexpression (HER-2+), and only 2 (12.5%) HER-2+ patients received trastuzumab therapy during progression. Three additional HER-2+ patients added trastuzumab after PD. Of these patients, 2 patients exhibited PR, and 1 patient exhibited cCR, which was confirmed as pCR after surgery.

Progression was diagnosed after one cycle ($n = 1$), two cycles ($n = 17$), three cycles ($n = 8$), four cycles ($n = 11$), five cycles ($n = 2$), six cycles ($n = 3$) and eight cycles ($n = 3$). The median number of cycles was 3. Tumor progression was observed in 41 (91.1%) patients. Nodal progression was observed in 5 (11.1%) patients, and distant metastasis was observed in 3 (6.7%) patients. As shown in Figure 1, 28 (62.2%) patients received a mastectomy immediately after PD, and 17 (37.8%) changed chemotherapy. After changing to a second chemotherapy, 7 patients still exhibited PD, 3 patients had SD, 7 patients had PR, and 1 patient exhibited a pCR after surgery. Compared with the 28 patients who switched to surgery immediately after PD and 17 patients who switched to a different chemotherapy regimen, no statistically significant differences in OS and DFS were between these two salvage therapies (Figure 2a,b).

Comparison of tumor characteristics between PD and pCR patients

Patients with PD were also compared with patients with pCR after surgery (Table 2). A pathologic complete response in both the breast and axilla occurred in 133 (11.2%) of all NACT patients (including one PD patient who changed chemotherapy after PD was noted and exhibited pCR after surgery). No significant differences were noted in age, menopausal status, family history of cancer, body mass index (BMI), prechemotherapy T stage, prechemotherapy AJCC stage, nuclear grade, Topoisomerase (TOPO) II, Ki-67 score, ER status, PR status, Her-2 status, and surgery type. The following pretreatment tumor features were different: pretreatment tumor size (with median size, 38 mm vs. 31 mm, $p = .015$) and pretreatment T stage ($p < .001$). In total, 48.9% of PD patients had pretreatment T3-4 tumors, whereas 72.2% of pCR patients had pretreatment T2 tumors. Histological type also differed ($p < .001$). Only 34 (75.6%) tumors in PD patients were classified as ductal type, whereas 127 (95.5%) pCR patients exhibited this type of disease. Pretreatment chemotherapy features that exhibited significant differences included taxane-based regimen ($p < .001$) and trastuzumab-based regimen ($p < .001$). Of the 116 HER2+ patients receiving trastuzumab-containing regimens, 2 (1.72%) had PD, and 40 (34.48%) had pCR. Of the 317 HER2+ patients receiving NACT without trastuzumab, 14 (4.42%) had PD and 24 (7.57%) had pCR (Figure 3a). Additionally, tumor subtypes were evaluated (Figure 3b). Of the 234 patients with hormone receptor (HR)+ and HER-2

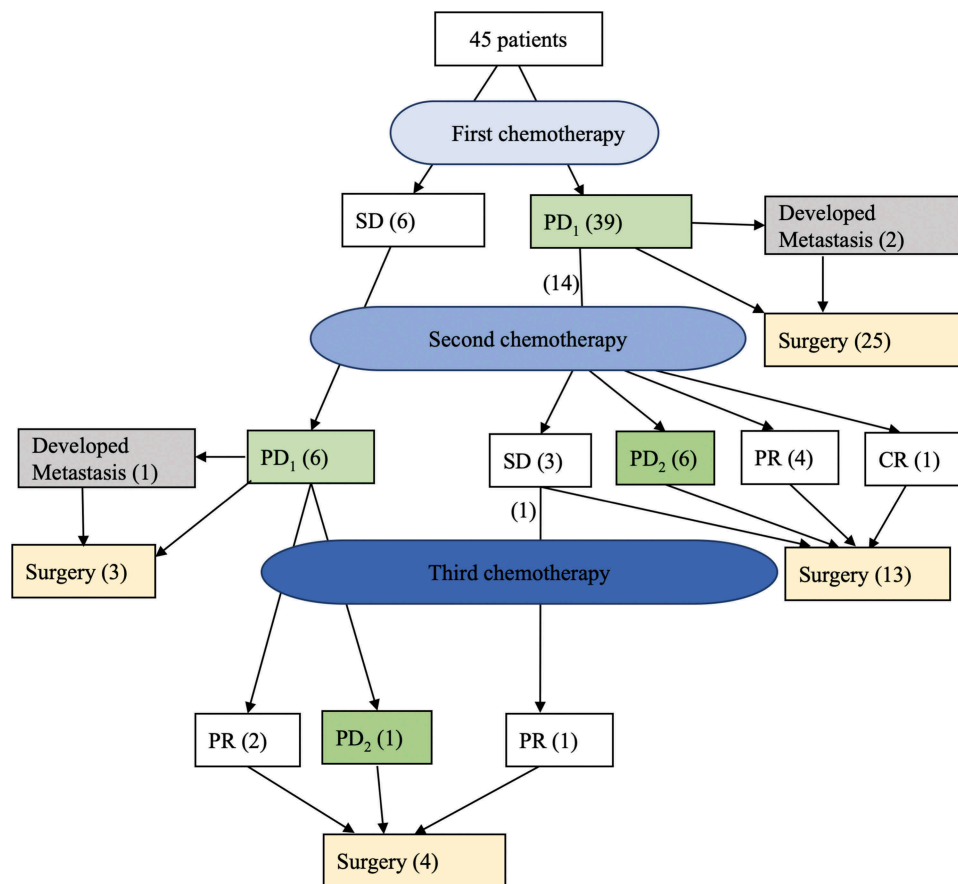


Figure 1. Timing of PD/SD/response on NACT.

+ tumors, 4 (1.71%) patients had PD and 32 (13.68%) patients had pCR. Of the 383 patients with HR+ and HER-2- disease, 9 (2.35%) patients had PD and 23 (6.01%) patients had pCR. Of the 198 patients with HR- and HER-2+ tumors, 12 (6.06%) patients had PD and 32 (16.16%) patients had pCR. Of the 207 patients with HR- and HER-2- tumors, 12 (5.80%) patients had PD and 30 (14.49%) patients had pCR. Patients with pCR exhibited significantly longer OS and DFS compared with patients with PD (Figure 2c,d)

Predictors of PD

Predictors of tumor progression are listed in Table 3. In univariate analysis, predictors of PD included prechemotherapy tumor size ($P = .044$), prechemotherapy T stage ($P = .009$), ER negative ($P = .001$), PR negative ($P = .009$), high nuclear grade ($P = .001$), high Ki-67 score ($P = .001$), mixed or other histology types ($P < .001$), and non-taxane based regimen ($P < .001$). In multivariate analysis, significant predictors of progression including nuclear grade 3 (OR = 5.05; 95% CI, 1.18 to 21.61; $P = .029$) and high Ki-67 score (OR = 1.03; 95% CI, 1.00 to 1.06; $P = .047$).

Survival analysis

The median follow-up time of OS and DFS was 45.47 months (range, 0.80 to 140.53 months). The OS rates determined by Kaplan-Meier analysis for the PD and non-PD groups are

presented in Figure 2e. The median OS time was 64.40 months in patients with PD and was not achieved in the non-PD group. Factors significantly affecting OS (listed in Table 4) in univariate analysis were PD (HR 3.85, $P < .001$), BMI (HR 0.95, $P = .015$), prechemotherapy size (HR = 1.02, $P < .001$), prechemotherapy T3 and T4 stage (with T3 HR = 3.12, $P = .002$ and T4 HR = 2.94, $P = .003$), prechemotherapy N3 stage (HR 4.17, $P < .001$), prechemotherapy IIIB/IIIC stage (HR = 4.23, $P < .001$), ER positive (HR = .59, $P < .001$), PR positive (HR = .61, $P = .001$), lymphovascular invasion (HR = 2.09, $P < .001$), nuclear grade 3 (HR = 10.88, $P = .019$) and trastuzumab therapy (HR = .39, $P = .009$). In multivariate analysis, PD (HR = 3.85, $P = .001$), prechemotherapy size (HR = 1.01, $P = .035$), prechemotherapy N3 stage (HR = 3.07, $P = .032$), ER positive (HR = .42, $P = .001$), and trastuzumab therapy (HR = 0.10, $P = .023$) were predictive of OS. The DFS rates based on Kaplan-Meier analysis for the PD and non-PD groups are presented in figure 2f. The median DFS time was 25.30 months in the patients with PD and was not achieved in the non-PD group. Factors affecting DFS (listed in Table 4) in univariate analysis were PD (HR 3.00, $P < .001$); BMI (HR = .96, $P = .036$); prechemotherapy size (HR = 1.02, $P < .001$); prechemotherapy T3 and T4 stage (with T3 HR = 2.89, $P < .001$ and T4 HR = 2.55, $P = .001$); prechemotherapy N1, N2 and N3 stage (with N1 HR = 1.52, $P = .041$, N2 HR = 1.74, $P = .016$ and N3 HR = 4.70, $P < .001$); prechemotherapy IIB/IIIA and IIIB/IIIC stage (with IIB/IIIA HR = 2.01, $P = .002$ and IIIB/IIIC HR = 4.57, $P < .001$); ER

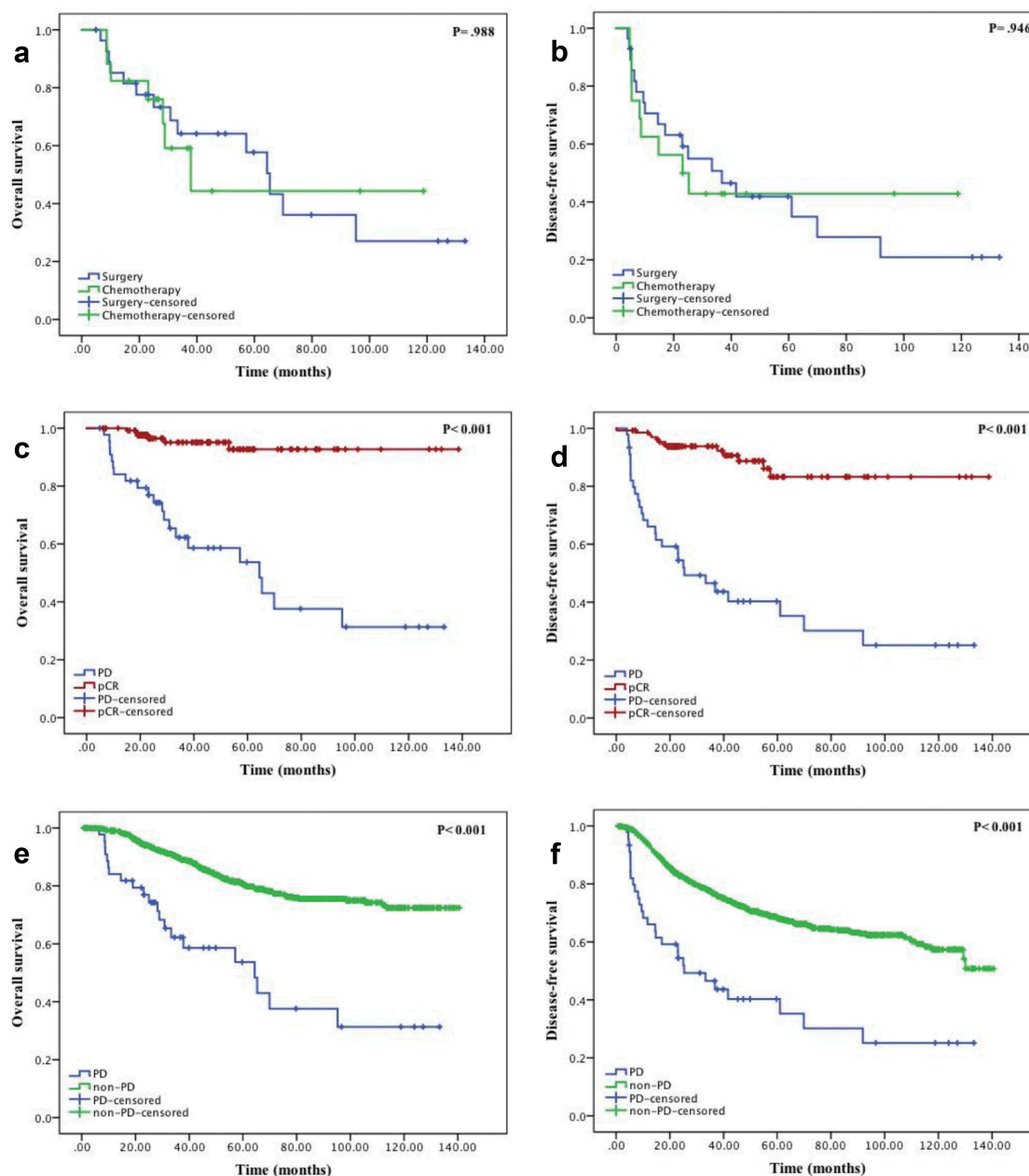


Figure 2. (a) Overall survival of the two salvage therapies (surgery and chemotherapy). (b) Disease-free survival of the two salvage therapies (surgery and chemotherapy). (c) Overall survival and (d) disease-free survival of patients with progression disease (PD) and pathological complete response (pCR). (e) Overall survival and (f) disease-free survival of patients with PD and non-PD.

positive (HR = .68, $P < .001$); PR positive (HR .66, $P < .001$); lymphovascular invasion (HR 1.99, $P < .001$); nuclear grade 3 (HR 4.13, $P = .018$); Ki-67 index score (HR = 1.01, $P = .028$); and trastuzumab therapy (HR = .55, $P = .006$). In multivariate analysis, factors that were predictive for DFS included PD (HR = 3.77, $P = .001$), prechemotherapy size (HR 1.02, $P = .010$), prechemotherapy N3 stage (HR 3.14, $P = .040$), ER positive (HR = .47, $P = .002$) and lymphovascular invasion (HR = 1.90, $P = .008$).

Discussion

In this study, we described predictors of progression during NACT in China. To our knowledge, this is the largest study to

date on PD during NACT in Asian patients. In China, statistical results about NACT are rarely studied or recorded by researchers, and considerably less is known about NACT in China compared with Western countries. Therefore, we collected detailed information on factors that might influence NACT response.

PD occurs in 3 – 6% in NACT cases.^{5,7} This finding is in accordance with our study. The pretreatment predictors of disease progression include large tumor size, T stage, ER and PR negativity, high Ki-67 scores, and high nuclear grade. All these results are similar to the study performed at the MD Anderson Cancer Center by Caudle et al.⁵ In contrast to other reports, our study discovered that in addition to ductal and lobular histology, PD tumors exhibited increased

Table 2. Patients' and tumor characteristics of PD and pCR.

Factor	PD (n = 45, 3.8%)		pCR (n = 133, 11.2%)		P
	No. of Patients	%	No. of Patients	%	
Age, years					.352
Median	48		49		
Range	21–65		26–69		
Menopausal status					.142
Premenopausal	30	66.7	61	45.9	
postmenopausal	15	33.3	72	54.1	
Family history of cancer					.154
Breast cancer	1	2.2	8	6.1	
Other cancers	6	13.3	31	23.3	
No	38	84.4	94	70.7	
BMI					.517
Median	23.191		23.437		
Range	14.9–30.8		16.61–31.64		
Tumor size, mm					.015
Median	38.0		31.0		
Range	13.0–130.0		9.0–145.0		
T stage					<.001
T1	4	8.9	16	12.0	
T2	19	42.2	96	72.2	
T3	13	28.9	13	9.8	
T4	9	20.0	8	6.0	
N stage					.553
N0	7	15.6	20	15.0	
N1	27	60.0	68	51.1	
N2	7	15.6	34	25.6	
N3	4	8.9	11	8.3	
AJCC stage					.289
IA/IIA	8	17.8	26	19.5	
IIB/IIIA	26	57.8	88	66.2	
IIB/IIIC	11	24.4	19	14.3	
Histology					<.001
Ductal	34	75.6	127	95.5	
Lobular	2	4.4	1	0.8	
Mixed	5	11.1	0	0.0	
Other	4	8.9	2	1.5	
Unknown	0	0.0	3	2.3	
Nuclear grade					.549
I	0	0.0	0	0.0	
II	4	8.9	6	4.5	
III	14	31.1	10	7.5	
Unknown	27	60.0	117	88.0	
TOPO II					.637
Negative	3	6.7	4	3.0	
Positive	25	55.6	68	51.1	
Unknown	17	37.8	61	45.9	
Ki-67 score ^a					.130
Median	50.00		40.00		
Range	5–90		1–90		
ER status					.477
Negative	31	68.9	80	60.2	
Positive	14	31.1	47	35.3	
Unknown	0	0	6	4.5	
PR status					.986
Negative	32	71.1	88	66.2	
Positive	13	28.9	38	28.6	
Unknown	0	0.0	7	5.3	
Her-2					.149
Negative	21	46.7	53	39.8	
Positive	16	35.6	64	48.1	
Uncertain	6	13.3	8	6.0	
Unknown	2	0	8	6.0	
Chemotherapy regimen					.565
Anthracycline-based	37	82.2	104	78.2	
Taxane-based	31	68.9	127	95.5	<.001
Trastuzumab	2	4.4	42	31.6	<.001
Surgery					.542
BCT	1	2.2	8	6.0	
Mastectomy	44	97.8	125	94.0	

Abbreviations: PD, progressive disease; pCR, pathological complete response; BMI, body mass index; AJCC, American Joint Committee on Cancer; TOPO, topoisomerase; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2; BCT, breast-conserving therapy.

^aKi-67 scores were available in 27 patients in the PD group and 107 patients in the pCR group.

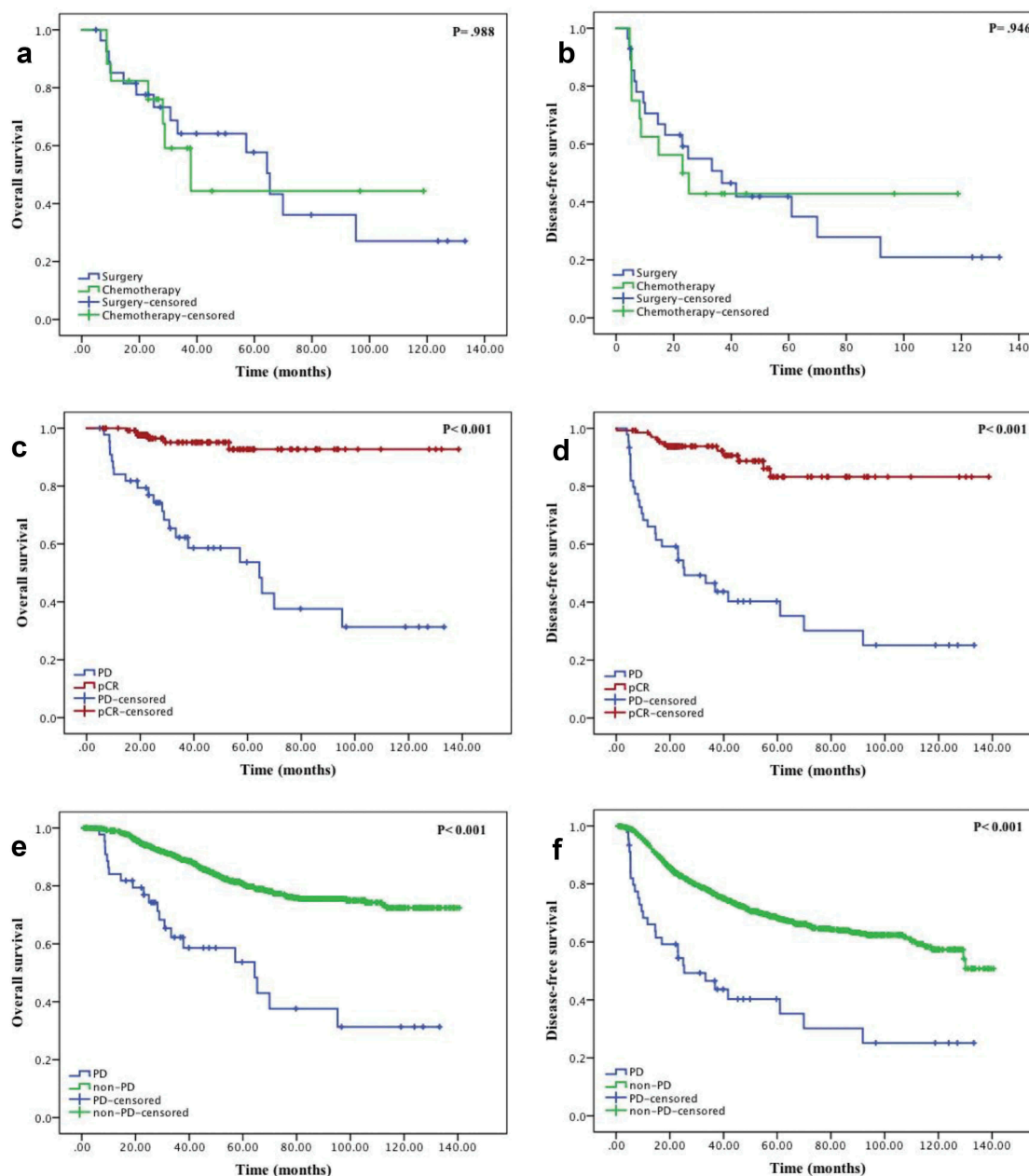


Figure 3. (a) Tumor response in HER2+ patients receiving NACT with or without trastuzumab. (b) Evaluation of tumor response in different tumor subtypes.

proportions of mixed and other special types of histology compared with the non-PD group as mentioned above. Compared with invasive ductal carcinoma and invasive lobular carcinoma, these special types of breast carcinoma exhibit a more aggressive behavior. These carcinomas exhibit an increased propensity of local and distant recurrence and poorer overall survival and disease-free survival regardless of similar age and disease stages at presentation and the relative proportion of these special carcinoma components.¹³⁻¹⁶ For instance, invasive micropapillary carcinoma of the breast exhibited increased frequencies of lymphovascular invasion and lymph nodal metastasis.¹⁷ Merino et al. reported that primary signet ring cell carcinoma-related death occurred in 60% of 24 patients within 7 years.¹⁶ Standard chemotherapy is typically unsuccessful in the treatment of these patients.^{13,18,19} The study by

Tanabe et al.²⁰ revealed that 82% of MPCs experienced PD during NACT. Hennessy et al.²¹ reported that metaplastic sarcomatoid carcinomas were less sensitive to primary anthracycline/taxane-based chemotherapy compared with that reported in conventional breast adenocarcinoma. Chen et al.²² demonstrated that none of the MPCs patients who received anthracycline, vinorelbine, or cyclophosphamide-based chemotherapy responded, and only 17.6% of patients who received taxane-based chemotherapy exhibited a partial response. The above information potentially suggests that therapies other than regular NACT may be suggested when we encounter these special types of histology.

Currently, there is no standard treatment protocol for PD given the low rate and the rarity of large prospective clinical studies. In our study, 28 patients switched to surgery immediately after PD, and 17 patients switched to a different

Table 3. Predictors of PD.

Factor	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age	0.98 (0.95, 1.02)	.325		
BMI	0.96 (0.87, 1.05)	.341		
Family history of cancer		.498		
No	1.00	-		
Breast cancer	0.62 (.08, 4.64)	.642		
Other cancers	0.61 (0.25, 1.45)	.266		
Menopausal status		-		
Premenopausal	1.00	-		
Postmenopausal	0.65 (0.35, 1.22)	.183		
Prechemotherapy size	1.01 (1.00, 1.03)	.044		
Prechemotherapy		.009		
T stage		-		
T1	1.00	-		
T2	0.48 (0.16, 1.45)	.19		
T3	1.57 (0.50, 4.99)	.441		
T4	1.19 (0.35, 3.98)	.782		
Prechemotherapy		.790		
N stage		-		
N0	1.00	-		
N1	0.80 (0.34, 1.87)	.604		
N2	0.61 (0.21, 1.79)	.369		
N3	0.61 (0.18, 2.14)	.442		
Prechemotherapy		.474		
AJCC stage		-		
IA/IIA	1.00	-		
IIB/IIIA	0.61 (0.27, 1.38)	.237		
IIIB/IIIC	0.77 (0.30, 1.95)	.576		
ER status		-		
Negative	1.00	-		
Positive	0.32 (0.17, 0.61)	.001		
PR status		-		
Negative	1.00	-		
Positive	0.42 (0.22, 0.81)	.009		
HER2 status		-		
Negative	1.00	-		
Positive	1.03 (0.53, 2.00)	.928		
Histology		<.001		
Ductal	1.00	-		
Lobular	4.24 (0.93, 19.26)	.062		
Mixed	11.35 (3.87, 33.30)	.000		
Others	5.52 (1.81, 16.85)	.003		
Nuclear grade		-		
1/2	1.00	-	1.00	-
3	7.03 (2.26, 21.83)	.001	5.05 (1.18, 21.61)	.029
Ki-67 score	1.03 (1.01, 1.04)	.001	1.03 (1.00, 1.06)	.047
Anthracycline-based regimen	0.57 (0.26, 1.26)	.166		
Taxane-based regimen	0.22 (0.11, 0.42)	<.001		
Trastuzumab therapy	0.41 (0.10, 1.70)	.219		

Abbreviations: PD, progressive disease; OR, Odds Ratio; BMI, body mass index; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

chemotherapy. For the 17 patients who changed chemotherapy regimens, 10 (58.8%) patients continued to exhibit PD or SD (Figure 1). Furthermore, the addition of taxane to an anthracycline-based regimen, particularly when added sequentially, was confirmed to result in increased response rates, DFS and OS in breast cancer patients.^{23,24} In this study, after experiencing no response to the EC regimen (either SD or PD), 9 patients added taxane sequentially. Only 1 patient had PR, and the remaining 8 patients continued experienced PD. All these results suggest that patients whose tumors do not exhibit a response to first-line chemotherapy may not exhibit further tumor size shrinkage as a result of any further changes or additions to the chemotherapy regimen. Other neoadjuvant trials also confirmed this phenomenon. Both the GeparTrio phase III trial²⁵ and the Aberdeen trial^{26,27}

demonstrated that compared with the early responders to chemotherapy, switching the early chemotherapy of nonresponders to a different chemotherapy regimen before surgery did not result in the achievement of pCR. Furthermore, we did not observe statistically significant differences in either DFS or OS between patients undergoing surgery or changing chemotherapy after PD (Figure 2a,b). Based on all these results, we conclude that once a patient experiences PD, surgery should be suggested instead of further chemotherapy.

Breast cancer is a clinically heterogeneous disease; thus, not all breast cancer patients respond equally to chemotherapy and exhibit the same prognoses. Most patients experience clinical responses, with the rate ranging from 50 to 90%. A small number of patients experience pCR after surgery, and rates ranged from 2 to 27%. An even smaller number of patients (approximately 2-5%) experience PD during treatment.^{28,29} This study implied that tumor characteristics that correlated with progression were also associated with the likelihood of a complete response to NACT.⁵ However, PD and pCR had two polarizing prognoses. The long-term data from National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 and B-27 demonstrated that the achievement of pCR in both breast and axillary nodes after NACT clearly predict favorable long-term outcomes.⁴ In contrast, once patients experience PD, they may incorrectly perceive a risk in delaying surgery or even losing the opportunity for operation. The characteristics and clinical outcomes of PD compared with pCR have not been reported to date. In this study, we compared the characteristics of these two groups of patients. As presented in Table 2, our study revealed no differences in age, menopausal status, family history of cancer, BMI, pretreatment N stage, AJCC stage, nuclear grade, TOPO II, ER expression, PR expression, HER-2 expression, anthracycline-based chemotherapy and types of surgery between PD and pCR patients. Chemotherapy regimens based on taxane exhibited significance ($P < .001$) (also see the difference in the comparison between PD and non-PD group) because PD occurred within 4 cycles of NACT in 37 (82.2%). These patients may transfer to surgery or other salvage chemotherapies and thus do not use taxane-based sequential therapy. A neoadjuvant combination of trastuzumab and chemotherapy resulted in an increased pCR rate in HER-2+ primary breast cancer.³⁰ In this study, a chemotherapy regimen based on Trastuzumab also exhibited significance ($P < .001$). As shown in Figure 3a, of the HER-2+ patients not receiving trastuzumab, 4.42% had PD and 7.57% had pCR. However, of the HER-2+ patients receiving trastuzumab, only 1.72% had PD and 34.48% had pCR. Moreover, after administering trastuzumab to HER-2+ PD patients, the patients experienced further PR, and some patients even achieved pCR after surgery. This finding suggests that the addition of trastuzumab to NACT may benefit HER-2+ patients. Once a HER-2+ patient experiences PD during NACT, the addition of trastuzumab instead of changing the chemotherapy regimen might result in an increased tumor response. It is noteworthy that although PD patients presented with a significantly higher Ki-67 index compared with the non-PD group ($P = .01$, as shown in Table 1), no significant difference in Ki-67 index values are noted between PD and pCR patients. Both groups exhibit

Table 4. Univariate and multivariate effects of potentially prognostic factors on OS and DFS.

Prognostic factor	Predictors of Overall survival				Predictors of Disease-free survival			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Response status								
Non-PD	1.00	-	1.00	-	1.00	-	1.00	-
PD	3.85 (2.45, 6.05)	<.001	3.85 (1.77, 8.35)	.001	3.00 (2.04, 4.42)	<.001	3.77(1.77, 8.00)	.001
Age	0.99 (0.98, 1.02)	.855			0.99 (0.98, 1.01)	.176		
BMI	0.95 (0.90, 0.99)	.015			0.96 (0.93, 0.99)	.036		
Family history of cancer								
No	1.00	-			1.00	-		
Breast cancer	0.37 (0.12, 1.15)	.09			0.61 (0.30, 1.23)	.166		
Other cancers	0.76 (0.52, 1.11)	.159			0.86 (0.65, 1.13)	.284		
Menopausal status								
Premenopausal	1.00	-			1.00	-		
Postmenopausal	1.07 (0.81, 1.41)	.635			0.86 (0.70, 1.07)	.181		
Prechemotherapy size	1.02 (1.02, 1.03)	<.001	1.01 (1.00, 1.03)	.035	1.02 (1.02, 1.03)	<.001	1.02 (1.00, 1.03)	.010
Prechemotherapy T stage								
T1	1.00	-			1.00	-		
T2	1.16 (0.59, 2.29)	.673			1.17 (0.71, 1.92)	.544		
T3	3.12 (1.53, 6.34)	.002			2.89 (1.71, 4.88)	<.001		
T4	2.94 (1.44, 6.02)	.003			2.55 (1.50, 4.34)	.001		
Prechemotherapy N stage								
N0	1.00	-	1.00	-	1.00	-	1.00	-
N1	1.29 (0.77, 2.15)	.339	1.14 (0.44, 2.98)	.784	1.52 (1.02, 2.28)	.041	0.97 (0.34, 2.76)	.954
N2	1.49 (0.84, 2.64)	.175	1.21 (0.42, 3.44)	.727	1.74 (1.11, 2.72)	.016	1.54 (0.52, 4.60)	.437
N3	4.17 (2.39, 7.28)	<.001	3.07 (1.10, 8.58)	.032	4.70 (3.02, 7.33)	<.001	3.14 (1.05, 9.35)	.040
Prechemotherapy								
AJCC stage								
IA/IIA	1.00	-			1.00	-		
IIB/IIIA	1.77 (0.99, 3.14)	.052			2.01 (1.29, 3.11)	.002		
IIIB/IIIC	4.23 (2.35, 7.62)	<.001			4.57 (2.90, 7.19)	<.001		
ER status								
Negative	1.00	-	1.00	-	1.00	-	1.00	-
Positive	0.59 (0.45, 0.78)	<.001	0.42 (0.25, 0.72)	.001	0.68 (0.55, 0.84)	<.001	0.47 (0.29, 0.76)	.002
PR status								
Negative	1.00	-			1.00	-		
Positive	0.61 (0.46, 0.81)	.001			0.66 (0.54, 0.82)	<.001		
HER2 status								
Negative	1.00	-			1.00	-		
Positive	1.03 (0.77, 1.40)	.826			0.91 (0.73, 1.15)	.431		
Histology		.523						
Ductal	1.00	-			1.00	-		
Lobular	1.84 (0.68, 4.951)	.230			0.88 (0.33, 2.37)	.805		
Mixed	1.45 (0.64, 3.27)	.369			0.94 (0.44, 1.98)	.866		
Others	1.12 (0.50, 2.53)	.786			1.24 (0.68, 2.27)	.480		
Lymphovascular invasion								
Negative	1.00	-			1.00	-	1.00	-
Positive	2.09 (1.59, 2.76)	<.001			1.99 (1.61, 2.45)	<.001	1.90 (1.19, 3.05)	.008
Nuclear grade								
1	1.00	-	1.00	-	1.00	-		
2	4.26 (0.58, 31.21)	.154	4.24 (0.57, 31.44)	.158	2.58 (0.81, 8.22)	.110		
3	10.88 (1.48, 80.01)	.019	6.12 (0.80, 46.68)	.080	4.13 (1.28, 13.32)	.018		
Ki-67 score	1.01 (0.99, 1.01)	.197			1.01 (1.00, 1.01)	.028		
Anthracycline-based regimen	1.46 (0.83, 2.56)	.188			1.06 (0.73, 1.55)	.758		
Taxane-based regimen	1.28 (0.63, 2.59)	.498			1.40 (0.81, 2.44)	.233		
Trastuzumab therapy	0.39 (0.19, 0.79)	.009	0.10 (0.01, 0.73)	.023	0.55 (0.35, 0.84)	.006		

Abbreviations: HR, Hazard Ratio; PD, progressive disease; BMI, body mass index; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

a median Ki-67 index > 40%. Ki-67 is present in all proliferating cells and serves as a proliferation marker.³¹ Several retrospective studies confirmed that an increased Ki67 index is associated with an increased pCR rate.^{32,33} Simultaneously, some studies reported that high Ki67 correlated with progressive disease.⁵ Our results are consistent with previous studies, suggesting that patients with a risk of progression are also more likely to exhibit a complete response to NACT. This finding suggests that high cell proliferation might exhibit a bilateral relation to chemosensitivity. However, this result is not as obvious in reports that suggest it directly reflects achieving pCR.³⁴

Different subsets of breast cancers have different degrees of chemotherapy sensitivity.³⁵ In this report, we studied the response of different tumor subtypes to therapy. As shown in Figure 3b, the HR-/HER-2+ subgroups exhibited the highest rates of both PD and pCR. The PD rate was lowest in the HR+/HER-2+ subgroup, and the pCR rate was lowest in the HR+/HER-2- subgroup. This effect has also been observed in the study by Caudle et al.⁵ Although no additional studies about PD in subset groups were reported, the pCR rate was the highest in the HR-/HER2+ subset and lowest in HR +/HER-2- subset as confirmed in the I-SPY 1 TRIAL,³³ Neoadjuvant Lapatinib and/or Trastuzumab Treatment

Optimization (Neo ALTTO),³⁶ and Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation (NeoSphere).³⁷ When combining previous studies with our study, we conclude that patients who are at greatest risk of PD are more likely to exhibit pCR. However, compared with pCR patients, PD patients are more likely to present with a large tumor size and more advanced stages of disease at diagnosis. This finding suggests that we should be aware that HR-/HER-2+ subgroup tumors with larger tumor size or advanced T stages exhibit PD during NACT. Given that most PD occurred during the first few chemotherapy cycles, frequent and comprehensive inspection is required to prevent PD. Given that DFS and OS curves differed significantly between PD and pCR patients ($P < .001$), there is an urgent need to identify novel molecular markers to predict disease response to NACT, thus allowing more individuals to obtain a pCR and facilitating the identification of individuals with low or no benefit to NACT.

Compared with most Western countries, one striking feature about Asian patients is the age at diagnosis. The median age in our study was 49, and 57.3% of patients were premenopausal. This finding is in accordance with other studies in Asian countries, with the age between 40–50 years. In contrast, the peak age in Western countries is 10 years older, and greater than half of patients were perimenopausal/postmenopausal.^{5,9,38} Among patients who received NACT in our cancer center, 65.6% were T2 stage and 57.7% were N1 stage. Clinical stage at diagnosis was IIB-IIIA in 65.2% and IIB-IIIC in 22.3% patients. The diagnosis at later stages compared with Western countries may be attributed to poor health awareness and education, lack of good screening instruments and medical examination per-year for early diagnosis and treatment. Moreover, patients in our country exhibit fear and misunderstanding of cancer treatment and outcomes. Patients become pale at the mention of cancers and therefore miss the best time for treatment. In our study, the PD, SD and pCR rates are similar to the randomized trial of NSABP B-18,³⁹ which demonstrated PD, SD and pCR rates of 3%, 17% and 13%, respectively. However, the cCR rate in NSABP B-18 (36%) was increased compared with our study. This finding may be attributed to the fact that the B-18 trial only enrolled patients with operable and palpable breast cancer (T1-3 N0-1 M0). In contrast, in our study, greater than 22.3% of patients were inoperable. In our study, the 5-year OS and DFS was similar to that of NSABP B-18. The results presented above demonstrated that although differences in age, menopausal status, race, genetic variation, lifestyle, environmental factors, and stage of disease at diagnosis between Asian and Western countries as reported previously [10], the validity of NACT in our country was similar to that of Western countries. Of note, our NACT regimens and doses were based on Western standards. However, compared with Western countries, our patients presented with a smaller BMI index and later tumor stages. This finding suggests that individual treatment is necessary to obtain a better prognosis. The other striking data from our center is that the breast conservation rate after NACT was only 2.9%, and most patients experienced mastectomy (97.1%). The BCT rate was considerably reduced compared with other Western cancer centers.

Specifically, the BCT rate at the MD Anderson Cancer Center was greater than 30%.⁴⁰ This difference may be related to a combination of factors, including socioeconomic factors in our country, a lack of radiotherapy equipment, patient-surgeon interactions, cognition of breast-conserving surgery, and difficulty in achieving negative margins of the primary tumor after NACT.

Although the data presented in our cancer center cannot represent the entire country, these data provide some useful insights into PD patients in Asian countries. However, some limitations should be noted. First, this is a retrospective study, and the number of patients enrolled was small, resulting in an even small number of PD patients. Furthermore, some patient information was incomplete, such as Ki-67 index, nuclear grade and Her-2 status. Thus, it was difficult to properly assess these patients. Thus, the results should be interpreted with caution, and further well-designed studies are urgently needed.

Conclusion

In summary, we conclude that predictors of progression during NACT include prechemotherapy size, prechemotherapy T stage, HR-negative, histology with mixed or other types, nuclear grade 3, and high Ki-67 score. In multivariate analysis, significant predictors of progression including nuclear grade 3 and high Ki-67 score. PD patients were associated with significantly worse DFS and OS. Once patients experience PD during NACT, the addition of trastuzumab to HER-2 + patients instead of changing the chemotherapy regimen and proceeding to surgery or further chemotherapy is suggested. We also demonstrate that patients who are at greater risk of PD are more likely to experience pCR. We should be aware that HR-/HER-2+ subgroup tumors with larger tumor sizes or advanced T stages are likely to exhibit PD during NACT. Frequent and comprehensive inspection is needed to prevent PD in early chemotherapy cycles. The search for biological markers for PD at the molecular level is urgent to select the best treatments for patients.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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