




In-Breast Tumor Progression During Neoadjuvant Chemotherapy: Impact on and Factors Influencing Distant Recurrence-Free Survival

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ABSTRACT

Background. Most patients with breast cancer treated with neoadjuvant chemotherapy (NAC) experience clinical benefit, however, a small proportion progress. We aimed to characterize factors predicting in-breast tumor progression and impact on distant recurrence.

Patients and Methods. We reviewed all patients with clinical stage I–III breast cancer treated with NAC in 2006–2021 at our institution. We compared in-breast progressive disease (PD), defined as $\geq 20\%$ increase in tumor size, with stable disease (SD) or response. Distant recurrence-free survival (DRFS) was analyzed using the Kaplan–Meier method and Cox proportional hazards regression.

Results. Of 1403 patients, 70 (5%) experienced in-breast PD, 243 (17%) SD, 560 (40%) partial response (PR), and 530 (38%) breast pathologic complete response (breast pCR, ypT0/Tis). The rate of PD varied by tumor subtype (8% in HR+/HER2–, 5% TNBC, 2% HER2+, $p < 0.001$). With median 48 months follow-up, the rates of DRFS were significantly different according to clinical breast response as follows: PD 56%, SD 68%, PR 82%, or breast pCR 93%, $p < 0.001$. In patients with PD on multivariable analysis, post-NAC grade (adjusted HR 2.9, $p = 0.002$) and ypT3–4 category (adjusted HR 2.4, $p = 0.03$) were the strongest predictors of DRFS. Combining these factors, 23% had neither, 44% had one, and 33% had both, which stratified outcome in

PD with 3-year DRFS of 100%, 77%, and 30%, respectively ($p < 0.001$).

Conclusions. While in-breast PD during NAC is uncommon (5%), it predicts poor survival. Among patients with in-breast PD, post-NAC tumor grade and T category predict outcomes and may be useful to guide treatment escalation.

Keywords Progressive disease · Neoadjuvant chemotherapy · Distant recurrence-free survival · Breast cancer

Neoadjuvant chemotherapy (NAC) has emerged as an important component of breast cancer treatment. It allows for de-escalation of surgery with increased utilization of breast conservation and sentinel lymph node surgery by decreasing the burden of disease in the breast and axilla.^{1–4} However, the greatest advantage of NAC is likely the prognostic information gained from assessment of disease response.^{3,5–8} These factors have driven the increased use of NAC over time, most notably in patients with human epidermal growth receptor 2 (HER2) positive or triple negative breast cancer (TNBC).^{9,10}

The advantages for NAC over adjuvant chemotherapy are clear; however, not all patients who undergo NAC have tumor response and some experience disease progression. While progressive disease (PD) is uncommon (1.6–7.2%), uncertainty remains about which patients are most likely to develop PD and the best clinical management.^{11–17} Caudle et al. evaluated a cohort of 59 patients with PD between 1994 and 2007 and identified African American race, greater tumor (T) category, higher AJCC clinical stage, higher tumor grade, and ER/PR negative receptor status as factors predicting PD.¹¹ Progressive disease impacted operative

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plan in a small percentage of these patients (0.5%).¹² In a more recent cohort of 124 patients with PD identified from 2005 to 2015, triple negative receptor status was independently associated with a decrease in overall survival (OS) in patients with PD. Likewise, inflammatory breast cancer and triple negative receptor status were both independently associated with distant failure in this group.¹⁶

While the population of patients with PD is small, it is critical to identify clinical and pathological factors associated with an increased risk for PD so that this population may be more closely monitored during NAC and to identify alternative treatment approaches. The aim of this study was to characterize patients who experience in-breast PD and to evaluate the impact of in-breast PD on survival.

PATIENTS AND METHODS

With institutional review board approval, clinical and pathologic data from patients with stage I–III breast cancer who underwent NAC were identified from a prospectively maintained institutional database. Patients diagnosed from 2006 to 2021 were included. Patients treated with neoadjuvant endocrine therapy were excluded, as were those who did not undergo surgery at our institution. Demographic, clinicopathologic, and treatment data were extracted from patient charts and included for analysis. Tumor size on pre-treatment ultrasound, and/or magnetic resonance imaging (MRI) where available, were recorded for each patient. The largest estimated tumor size across all imaging modalities was used as the pre-NAC clinical tumor size for the purposes of defining in-breast response. Post-treatment pathologic tumor size was extracted from the final surgical pathology report. The percent change in tumor size between pre-NAC imaging size and the post-treatment pathologic tumor size was calculated for each patient. PD was identified in accordance with revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1), where PD was defined as $\geq 20\%$ increase in the sum of the diameter of the target lesion and an absolute increase of ≥ 5 mm and was limited to disease progression in the breast.¹⁸ We did not include patients with disease progression only in the regional nodes or outside of the breast and nodal basins if there was no progression in the breast. In this study, HR+ was defined as either estrogen receptor (ER) or progesterone receptor (PR) $\geq 1\%$. HER2 status was defined as 3+ on immunohistochemistry (IHC) or a positive result on fluorescence in situ hybridization (FISH).

All patients undergoing NAC were characterized by their in-breast tumor response to treatment. Response to treatment was defined using modified RECIST criteria focused only on response in the breast as complete pathologic response (pCR, ypT0/ypTis), partial response (PR, $\geq 30\%$ decrease), stable disease (SD, response $< 30\%$ or increase $< 20\%$), or

PD. Response to treatment was evaluated in relation to tumor receptor status [hormone receptor positive (HR+)/(HER2–), HER2+, or TNBC], clinical T category at time of initial diagnosis, tumor histology (invasive ductal, invasive lobular, mixed, or other), tumor grade, type of breast surgery, and type of axillary surgery.

Statistical Analysis

Data were summarized overall and by modified RECIST category using the median (range) for continuous variables and frequency (percentage) for categorical variables. The associations of baseline demographic and clinical factors with modified RECIST category were assessed using Wilcoxon rank-sum or chi-squared tests. A binary variable characterizing the patient as having PD versus not was modeled using univariate and multivariable logistic regression to identify baseline demographic and clinical factors associated with PD. To assess the impact of modified RECIST category on long-term oncologic outcome, the endpoint of distant recurrence-free survival (DRFS) was assessed. DRFS was defined as the months from surgery to first distant recurrence, death from any cause, or last follow-up in those without an event. DRFS was estimated using the Kaplan–Meier method and compared across modified RECIST categories using a log-rank test.

Univariate and multivariable Cox proportional hazards regression were used to assess factors associated with DRFS within the subset of patients with PD. Given the small sample size in the PD group, the Firth penalized likelihood bias-reduction method was applied to improve performance with sparse data. Variables included in multivariable models were chosen as the combination of variables yielding the best score statistic after consideration of all possible models of appropriate size given the number of events available. Analysis was performed using SAS (version 9.4, SAS Institute Inc., Cary, NC) and R software (version 4.2.2, www.R-project.org). Estimates were reported with 95% confidence intervals (CI) and *p* values < 0.05 were considered statistically significant.

RESULTS

Of 1403 patients who underwent NAC and definitive surgical management, 530 (38%, 95% CI 35–40%) had breast pCR, 560 (40%, 95% CI 37–43%) PR, 243 (17%, 95% CI 15–19%) SD, and 70 (5%, 95% CI 4–6%) had in-breast PD. Median age of the patients with PD was 51.5 years, with median clinical tumor size at diagnosis of 3.2 cm. A total of 63% (44/70) had cT3–4 disease, 70% (49/70) were cN+, and 51% (36/70) had grade 3 disease at time of diagnosis, prior to initiation of NAC. The demographic, clinical, and

TABLE 1 Demographic and clinical characteristics of $N=1403$ patients treated with neoadjuvant chemotherapy 2006–2021, overall and stratified by in-breast tumor response

	Breast pCR ($N=530$)	PR ($N=560$)	SD ($N=243$)	PD ($N=70$)	Total ($N=1403$)
Age					
Median (range)	50.2 (22.7–86.2)	50.7 (22.3–83.6)	53.0 (28.3–85.3)	51.5 (29.5–79.5)	51.1 (22.3–86.2)
Race, n (%)					
American Indian/Alaskan Native	4 (0.8%)	4 (0.7%)	1 (0.4%)	0 (0.0%)	9 (0.7%)
Asian	16 (3.1%)	19 (3.6%)	8 (3.4%)	1 (1.4%)	44 (3.2%)
Black or African American	19 (3.7%)	22 (4.1%)	5 (2.1%)	5 (7.2%)	51 (3.8%)
Native Hawaiian/Pacific Islander	0 (0.0%)	2 (0.4%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
White	478 (92.5%)	488 (91.2%)	219 (94.0%)	63 (91.3%)	1248 (92.2%)
Missing	13	25	10	1	49
Ethnicity, n (%)					
Not Hispanic or Latino	501 (97.7%)	528 (98.1%)	229 (97.9%)	69 (100.0%)	1327 (98.0%)
Hispanic or Latino	12 (2.3%)	10 (1.9%)	5 (2.1%)	0 (0.0%)	27 (2.0%)
Missing	17	22	9	1	49
BMI					
Median (range)	26.8 (16.8–54.7)	27.9 (16.8–65.0)	27.2 (16.2–56.8)	29.7 (18.4–47.5)	27.5 (16.2–65.0)
BMI category, n (%)					
< 25	193 (36.4%)	179 (32.0%)	83 (34.2%)	16 (22.9%)	471 (33.6%)
25–29.9	168 (31.7%)	172 (30.7%)	76 (31.3%)	22 (31.4%)	438 (31.2%)
30–34.9	82 (15.5%)	117 (20.9%)	54 (22.2%)	17 (24.3%)	270 (19.2%)
≥ 35	87 (16.4%)	92 (16.4%)	30 (12.3%)	15 (21.4%)	224 (16.0%)
Histology, n (%)					
IDC	486 (91.7%)	495 (88.4%)	204 (84.0%)	56 (80.0%)	1241 (88.5%)
ILC	9 (1.7%)	32 (5.7%)	19 (7.8%)	9 (12.9%)	69 (4.9%)
MIDLCL	32 (6.0%)	28 (5.0%)	18 (7.4%)	3 (4.3%)	81 (5.8%)
Other	3 (0.6%)	5 (0.9%)	2 (0.8%)	2 (2.9%)	12 (0.9%)
Tumor biopsy grade, n (%)					
1	11 (2.1%)	30 (5.4%)	18 (7.4%)	5 (7.1%)	64 (4.6%)
2	108 (20.5%)	229 (41.0%)	111 (45.9%)	29 (41.4%)	477 (34.2%)
3	407 (77.4%)	299 (53.6%)	113 (46.7%)	36 (51.4%)	855 (61.2%)
Missing	4	2	1	0	7
Clinical tumor diameter, cm					
Median (Range)	3.1 (0.1–26.8)	4.1 (0.4–15.0)	3.9 (1.1–17.0)	3.2 (0.7–16.0)	3.6 (0.1–26.8)
Clinical T category, n (%)					
cT0/Tis	7 (1.3%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	8 (0.6%)
cT1	72 (13.6%)	33 (5.9%)	14 (5.8%)	4 (5.7%)	123 (8.8%)
cT2	284 (53.6%)	277 (49.5%)	120 (49.4%)	22 (31.4%)	703 (50.1%)
cT3	115 (21.7%)	197 (35.2%)	77 (31.7%)	24 (34.3%)	413 (29.4%)
cT4a-c	13 (2.5%)	33 (5.9%)	24 (9.9%)	9 (12.9%)	79 (5.6%)
cT4d	39 (7.4%)	20 (3.6%)	7 (2.9%)	11 (15.7%)	77 (5.5%)
Clinical node status, n (%)					
cN0	233 (44.0%)	235 (42.0%)	95 (39.1%)	21 (30.0%)	584 (41.6%)
cN+	297 (56.0%)	325 (58.0%)	148 (60.9%)	49 (70.0%)	819 (58.4%)
Biologic subtype, n (%)					
HER2+	262 (49.4%)	158 (28.2%)	42 (17.3%)	8 (11.4%)	470 (33.5%)
HR+/HER2–	109 (20.6%)	269 (48.0%)	148 (60.9%)	45 (64.3%)	571 (40.7%)
TNBC	159 (30.0%)	133 (23.8%)	53 (21.8%)	17 (24.3%)	362 (25.8%)

IDC Invasive ductal carcinoma, MIDLCL Mixed invasive ductal lobular carcinoma, ILC Invasive lobular carcinoma, HR Hormone receptor, TNBC Triple negative breast cancer

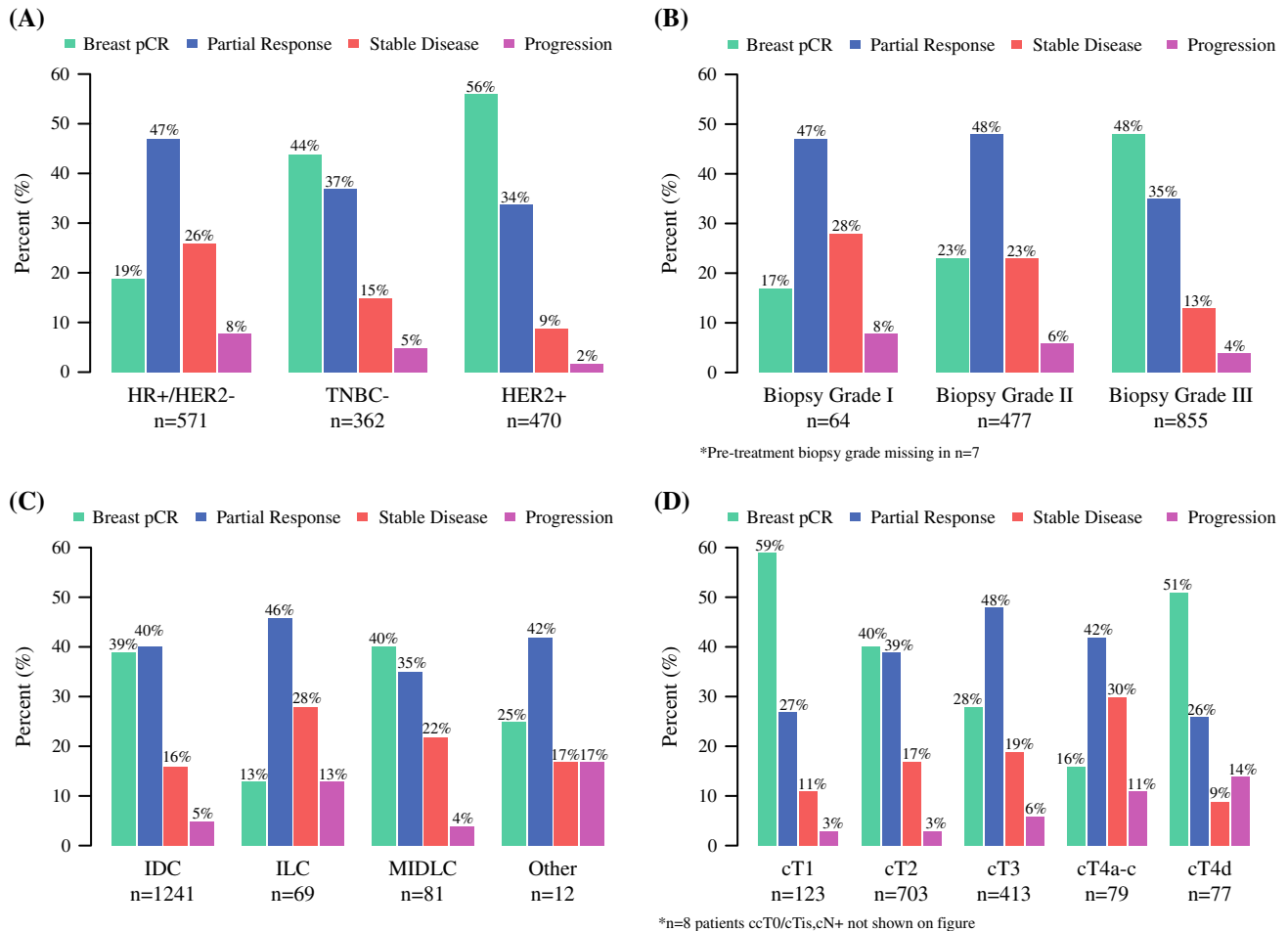


FIG. 1 Proportion of patients with either breast pCR, PR, SD, or PD based on **A** tumor biologic subtype, **B** tumor biopsy grade, **C** histology, and **D** clinical T category

pathologic data from the cohort overall and by modified RECIST category are summarized in Table 1.

Variables Associated with Response to NAC

Patients with breast pCR or PR were slightly younger than patients with SD or PD (median 50.5 versus 52.6 years, $p=0.005$). Regarding tumor biology, breast pCR rates were highest in HER2+ disease and TNBC at 56% and 44% compared with those with HR+/HER2- disease (breast pCR rate of 19%, $p<0.001$). PD was more common in HR+/HER2- disease (8% with PD) compared with HER2+ (2%) and TNBC (5%), $p<0.001$; see Fig. 1A. Furthermore, pre-treatment grade 1/2, invasive lobular or other histology, and higher cT category had higher rates of in-breast PD (see Fig. 1B–D). The most common other histology was metaplastic carcinoma, comprising 4/12 (33%), with 1/4 (25%) developing PD.

Looking at type of breast surgery performed, mastectomy rates were slightly higher in patients with in-breast PD (80%) compared with those with SD (76%), PR (73%), or breast pCR (70%), but this was not significant ($p=0.18$). Axillary surgery, however, was more extensive in patients with in-breast PD. Among clinically node negative (cN0) patients with in-breast PD, 33% underwent axillary lymph node dissection (ALND), while the rates of ALND in cN0 patients were 31% for SD, 17% for PR, and 7% for breast pCR, $p<0.001$. A majority of patients who were clinically node positive (cN+) at presentation underwent ALND in patients with in-breast PD, although a similar trend was observed across modified RECIST categories (88% for PD, 84% for SD, 78% for PR, 55% for breast pCR, $p<0.001$); see Fig. 2.

Factors Associated with In-Breast PD

On univariate analysis, factors associated with PD included clinical T3 or T4 category at diagnosis, histology,

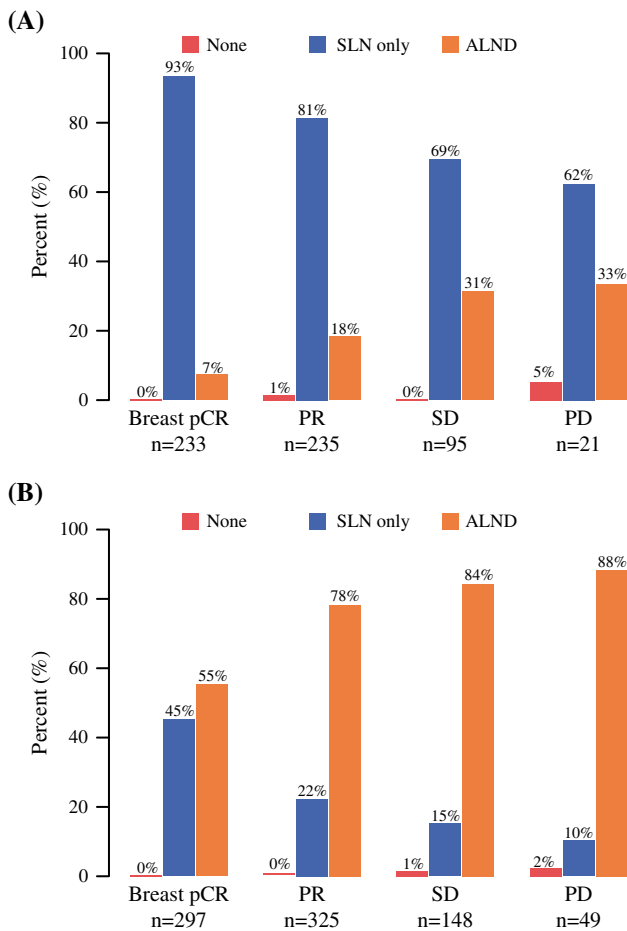


FIG. 2 Proportion of patients undergoing ALND when A cN0 or B cN+ stratified by response to treatment

and tumor subtype of HR+/HER2- or TNBC (Table 2). Patient age, body mass index (BMI), and biopsy tumor grade were not significantly associated with PD.

On multivariable analysis, factors associated with increased odds of PD were cT4 disease (adjusted odd ratio [aOR] 3.65, 95% CI 1.63–8.17, $p=0.002$ for cT4a–c and aOR 6.08, 95% CI 2.84–13.03, $p<0.001$ for cT4d, each versus cT0–2) and biologic subtype other than HER2+ disease (aOR 3.15, 95% CI 1.37–7.26, $p=0.007$ for TNBC and aOR 4.92, 95% CI 2.31–10.46, $p<0.001$ for HR+/HER2-, each versus HER2+), Table 2. Invasive ductal or mixed invasive ductal lobular carcinoma was associated with decreased odds of progression (aOR 0.44, 95% CI 0.22–0.91, $p=0.03$). This model showed good discrimination in identifying patients at higher risk for PD with area under the curve (AUC) of 0.72 (95% CI 66–78%) and adequate calibration (Hosmer–Lemeshow goodness-of-fit test $p=0.42$).

Distant Recurrence-Free Survival

With a median follow-up of 48 months, 36 patients with PD experienced a DRFS event, resulting in a DRFS estimate of 79% (95% CI 70–89%) at 1 year, 67% (95% CI 57–79%) at 3 years, and 56% (95% CI 45–70%) at 5 years. These 36 DRFS events included 32 patients with distant recurrence and 4 patients who died from other or unknown causes without breast cancer recurrence. The sites of first distant recurrence were as follows: bone (14), lung (9), liver (5), brain (3), distant lymph nodes (6), and other sites in 3, with 9 patients having multiple sites of first distant recurrence.

DRFS varied significantly ($p<0.001$) according to in-breast response to treatment (Fig. 3A). DRFS at 5 years was 93% (95% CI 90–95%) for patients achieving a breast pCR, 82% (95% CI 79–86%) for those with PR, and 68% (95% CI 62–76%) for SD, compared with the 56% (95% CI 45–70%) DRFS in those with PD at 5 years. When stratified by tumor biologic subtype, a stepwise decrease in DRFS was also observed to a degree within each subtype but with the clearest differentiation in patients with TNBC. Among patients with PD, DRFS was worst in patients with TNBC followed by those with HER2+ and HR+/HER2- breast cancer (Fig. 3B–D).

Factors Associated with DRFS in Patients with PD

DRFS in patients with PD did not differ by age ($p=0.48$), BMI ($p=0.87$), or ypN status ($p=0.84$). On univariate analysis, factors associated with DRFS in patients with PD included histology, biopsy tumor grade 3, post-NAC tumor grade 3, ypT3–4 category, and tumor; see Table 3.

On multivariable analysis, post-NAC grade 3 versus 1–2 [adjusted HR (aHR) 2.91, 95% CI 1.46–5.79, $p=0.002$] and ypT3–4 versus ypT1–2 category (aHR 2.44, 95% CI 1.10–5.40, $p=0.03$) were the strongest predictors of DRFS in patients with PD (Table 3). Combining these two factors, 23% (16/70) had neither, 44% (31/70) had one, and 33% (23/70) had both factors, which stratified outcome in the setting of PD with 3-year DRFS of 100%, 77% (95% CI 63–94%), and 30% (95% CI 16–56%), respectively ($p<0.001$); see Fig. 4. Although biologic subtype was not included directly in this model, the risk categories defined by post-NAC grade and ypT category were strongly related to tumor biologic subtype, with the two lowest risk groups predominantly HR+/HER2- disease [81% (13/16) and 87% (27/31), respectively] and with TNBC comprising >50% of the highest risk group (12/23); see Supplementary Fig. 1. Further, a large majority of HR+/HER2- patients with PD (40/45 or 89%) fell into the two lowest risk groups, while the majority of patients with HER2+ [75% (6/8)] and TNBC [71% (12/17)] with PD fell into the highest DRFS risk group.

TABLE 2 Univariate and multivariable logistic regression analysis evaluating factors associated with PD

	Univariate		Multivariable	
	Odds ratio (95% CI)	<i>p</i> Value	Odds ratio (95% CI)	<i>p</i> Value
Age, per 10-year increase	1.03 (0.84–1.26)	0.80	–	–
BMI category				
25–29.9 versus <25	1.50 (0.78–2.90)	0.22		
30–34.9 versus <25	1.91 (0.95–3.85)	0.07		
≥35 versus <25	2.04 (0.99–4.21)	0.05		
Histology				
IDC/MIDLC versus ILC/Other	0.30 (0.15–0.59)	<0.001	0.44 (0.21–0.91)	0.03
Tumor biopsy grade				
1–2 versus 3	1.52 (0.94–2.47)	0.09	–	–
Clinical T category				
cT3 versus cT0–2	1.92 (1.09–3.38)	0.02	1.60 (0.90–2.86)	0.11
cT4a–c versus cT0–2	4.00 (1.80–8.86)	<0.001	3.65 (1.63–8.17)	0.002
cT4d versus cT0–2	5.18 (2.45–10.95)	<0.001	6.08 (2.84–13.03)	<0.001
Biologic subtype				
HR+/HER2– versus HER2+	4.94 (2.31–10.59)	<0.001	4.92 (2.31–10.46)	<0.001
TNBC versus HER2+	2.85 (1.21–6.67)	0.02	3.15 (1.37–7.26)	0.007

IDC invasive ductal carcinoma, MIDLC mixed invasive ductal lobular carcinoma, ILC invasive lobular carcinoma, HR hormone receptor, TNBC triple negative breast cancer

DISCUSSION

In-breast disease progression during NAC is uncommon, and in this study occurred in 5% of patients. Patients with in-breast PD had significantly worse outcomes than those with breast pCR, PR, or SD. Our data demonstrate a significantly lower DRFS in patients with in-breast disease progression on NAC. Furthermore, among patients who do have PD, factors associated with poorer survival were post-NAC tumor grade 3 and residual breast tumor category of ypT3–4. Although DRFS in patients with PD was only 56% overall at 5 years, our analysis identified a subgroup of patients with PD, those with post-NAC grade 1–2 and ypT1–2, who had good DRFS during early follow-up despite their in-breast tumor progression during NAC.

Poorer DRFS in patients with PD is consistent with findings from prior studies including reports of DDFS of 23.2 months and 16 months.^{16,17} In comparison with those with PD, patients with breast pCR, PR, or SD in our cohort were found to have significantly better DRFS, further highlighting the critical relationship between response to NAC and overall outcomes. A systematic review and meta-analysis of 27,895 cases from 1999 to 2016 supports this finding and demonstrated that patients who achieved a pCR after NAC, compared with those who did not, experienced a significantly better event-free survival (EFS) and OS.¹⁹ This echoes findings published in an earlier international meta-analysis.²⁰ Furthermore, in a pooled analysis of 5161 patients from the USA and Europe from 2018 to 2019, residual cancer burden (RCB) score and class were independently

prognostic in all subtypes of breast cancer.⁸ A total of 38% of patients in our cohort achieved pCR, which is consistent with what has been published previously.²¹

The literature has demonstrated that response to NAC provides unique information about survival when stratified by tumor biologic subtypes. In particular, early data from the I-SPY1 clinical trial demonstrated that the extent of advantage conferred by pCR in terms of survival is specific to tumor biologic subtype.⁵ When looking more closely at pCR, multiple studies have demonstrated a survival benefit in patients experiencing pCR with HER2+ disease and TNBC.^{19,22,23}

Interestingly, in our cohort of patients with in-breast PD, we found that post-NAC tumor grade and T category were the strongest predictors of DRFS in patients with progressive disease, suggesting that survival in PD may be more heavily influenced by the way these features impact tumor response to NAC than tumor biologic subtype. However, the univariate significance of subtype and the strong relationship between subtype and post-NAC grade and ypT category, as well as the limitation of our small sample size with PD, suggest that subtype may be important, though we were unable to establish an independent association with DRFS in the setting of PD with this study.

The advent of targeted therapies for HER2+ disease as well as the use of immunotherapy for TNBC has changed the landscape of NAC. As trastuzumab and pertuzumab have been widely adopted in the neoadjuvant setting for HER2 positive disease, rates of pCR in this population have increased. An analysis of 6994 HER2+ patients included

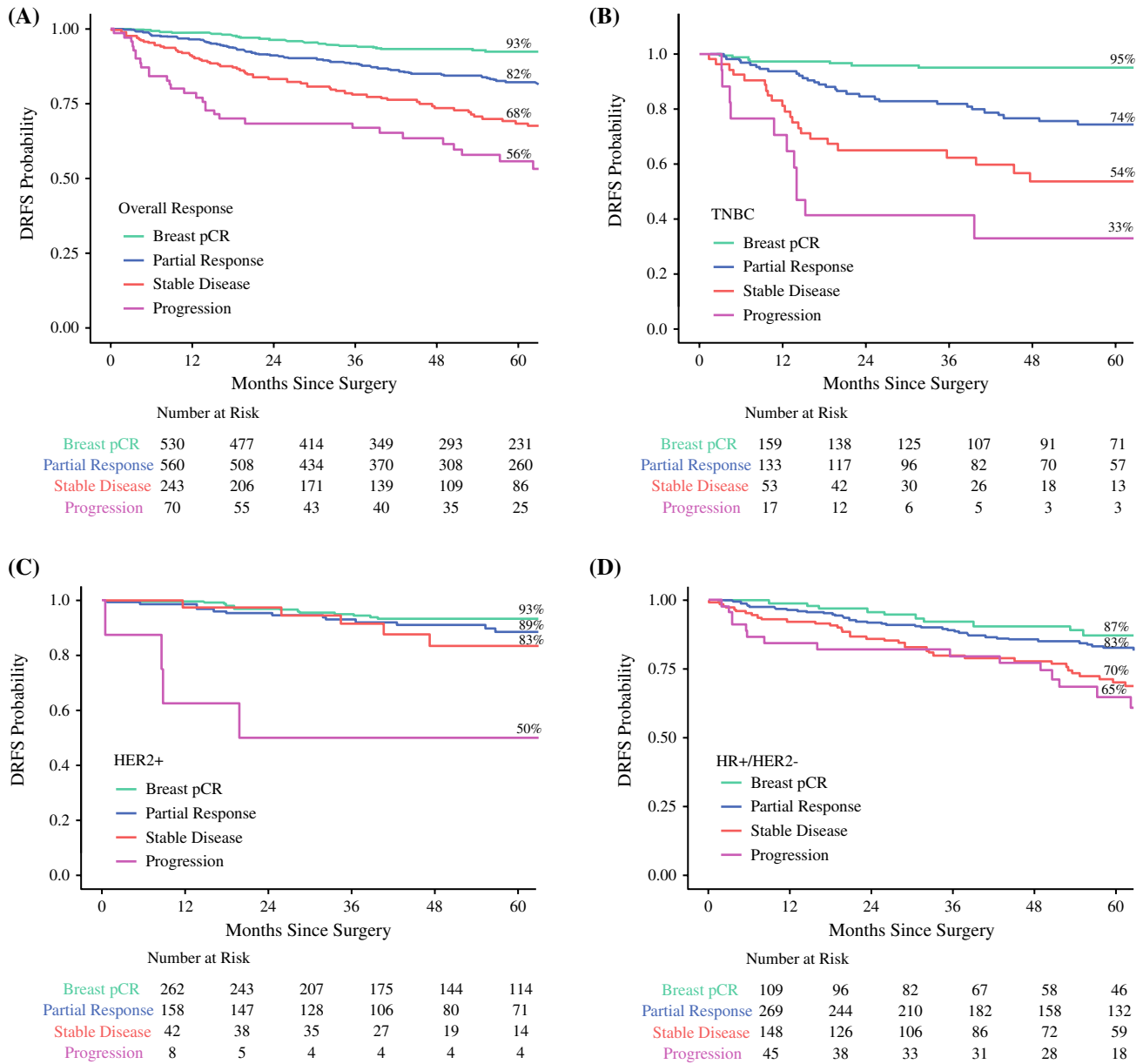


FIG. 3 Kaplan–Meier curve of distant recurrence-free survival (DRFS) through 5 years post-surgery in patients undergoing NAC based on response to treatment stratified by tumor biologic subtype

A overall, **B** in patients with TNBC, **C** in patients with HER2+ breast cancer, and **D** in patients with HR+/HER2- breast cancer

in the NCDB from 2013 to 2016 treated with multiagent HER2 directed chemotherapy in the neoadjuvant setting has demonstrated pCR rates as high as 46.6% in patients with cT1–T2/N0 disease.²⁴ When pCR was stratified by receptor subtype, this number rose to 63% in patients with HR–, HER2+ disease. Prospective studies have suggested that the number of patients achieving a pCR with multiagent HER2 directed chemotherapy in the neoadjuvant setting may be even higher.²⁵ In our cohort, the proportion of patients experiencing PD was lowest in those with HER2+ disease, which

is suggestive of the efficacy of targeted anti-HER2 NAC in patients with HER2+ disease.

While our cohort primarily captured patients prior to the wide adoption of targeted immunotherapy for TNBC, the last 2–3 years of our cohort included patients who received pembrolizumab as part of their neoadjuvant regimen as established by the KEYNOTE-522 trial. KEYNOTE-522 demonstrated a pCR rate of 60% in patients who received pembrolizumab in combination with chemotherapy in the neoadjuvant setting, compared with a pCR rate of 35–45% observed with conventional chemotherapy prior to adoption

TABLE 3 Univariate and multivariable Cox proportional hazards regression analysis of factors associated with DRFS among patients with in-breast progression ($n = 70$ patients with 36 DRFS events)

	Univariate		Multivariable	
	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value
Age, per 10-year increase	0.91 (0.70–1.19)	0.48	–	–
BMI, per 5-unit increase	0.98 (0.75–1.28)	0.87	–	–
Histology				
IDC/MIDLC versus ILC/other	0.44 (0.21–0.96)	0.04	–	–
Biopsy grade				
3 versus 1–2	2.15 (1.08–4.26)	0.03	–	–
Post-NAC grade				
3 versus 1–2	3.14 (1.58–6.24)	0.001	2.91 (1.46–5.79)	0.002
Pathologic T category				
ypT3–4 versus ypT1–2	1.92 (1.09–3.38)	0.02	2.44 (1.10–5.40)	0.03
Pathologic N status				
ypN+ versus ypN0	1.10 (0.46–2.61)	0.84	–	–
Biologic subtype				
HER2+ versus HR+/HER2–	2.26 (0.84–6.07)	0.11	–	–
TNBC versus HR+/HER2–	2.92 (1.37–6.21)	0.005	–	–

IDC Invasive ductal carcinoma, MIDLC Mixed invasive ductal lobular carcinoma, ILC Invasive lobular carcinoma, HR Hormone receptor, TNBC Triple negative breast cancer

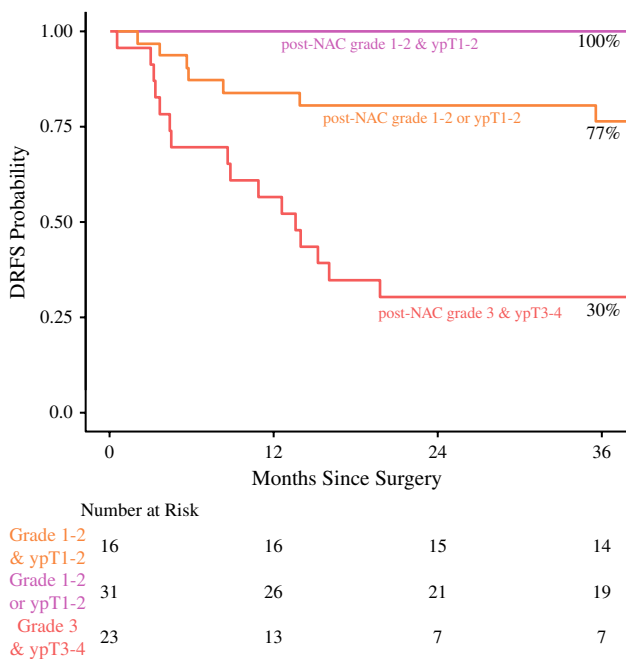


FIG. 4 Kaplan–Meier curve demonstrating post-NAC grade and ypT category together as predictors of DRFS in patients with in-breast tumor progression

of this NAC regimen in patients with TNBC.^{22,26} A smaller proportion of patients with TNBC in our study cohort experienced PD, though it is difficult to attribute this smaller proportion of patients exclusively to the inclusion of immunotherapy in NAC regimens. Future evaluation of cohorts who develop PD will better elucidate the impact that these

new therapies have had on the proportion of patients with TNBC developing PD.

Clinical T4 category and HR+/HER2– or TNBC tumor biology were associated with increased odds of disease progression on multivariable analysis in our cohort. We found that patients with T4a–c or T4d (inflammatory breast cancer) disease were more likely to experience disease progression. While this factor has been suggested in correlation with PD in previous studies, its predictive relationship has not been well characterized prior to this cohort. In particular, T4d category has been demonstrated to have significant impact on DFS and OS in previous studies, though it has not previously been identified as an independent predictor of PD prior to our cohort.¹⁶

With regard to biologic subtype, HR+/HER2– and TNBC were found to be independent predictors of PD in our cohort. Interestingly, this is the first cohort to identify HR+/HER2– biologic subtype as an independent predictor of PD. A previously published cohort examining patients from 1994 to 2007 demonstrated TNBC as an independent predictor of PD, which was also reflected in our cohort.¹¹ We anticipate that in future cohorts the proportion of patients with TNBC who experience progression may diminish due to recent advances in targeted NAC regimens in this group. While we have presented a more modern cohort in this study, the cohort was not recent enough to adequately capture these shifts in treatment.

We exclusively examined patients with PD who underwent surgery in this study and thus excluded patients who progressed and did not undergo surgical resection either due to disease extent, comorbidities, or development of

metastatic disease. While this facet of our study provided an interesting window into how breast-specific progression impacts DRFS, a limitation of this approach is that we did not examine progression in the regional nodes or distant progression during NAC. Future studies examining in-breast progression with regional nodal and distant progression may provide more insight into the facets of disease biology and histology that influence progressive disease outside the breast.

There are several other limitations to our study. Firstly, we utilized preoperative imaging size to estimate pretreatment tumor size. The type of imaging used to estimate pretreatment tumor size varied between patients, as we were not able to standardize imaging modalities due to the retrospective nature of our study design. Secondly, imaging after neoadjuvant treatment was not factored into our assessment of progression and was not routinely performed in our patient cohort. Thirdly, there was a very small number of patients with PD in our cohort, which could have affected the precision of our estimates of DRFS and limited our statistical power to detect factors associated with DRFS. As a result, our model could have excluded clinically important factors that were less common or had a smaller effect size. Fourthly, the small number of patients with PD means that our model for predicting DRFS may be overfit to this particular dataset. While we have tried to avoid this by including a number of variables considered reasonable for model stability given the number of events and by using penalized regression methods appropriate for sparse data, this model should be validated in other datasets.

Our study identified that 5% of patients develop progression, which is in congruence with prior recent studies identifying 1.6–7.2% of patients with progression.^{11–17} We anticipate that our rate of patients with progression was slightly higher than other studies as we strictly adhered to modified RECIST criteria utilizing final pathologic measurement of the tumor in defining the post-NAC tumor size. This comparison may have identified patients with subclinical progression who did not have PD noted on post-NAC, preoperative imaging. We anticipate that including patients with subclinical progression in our PD cohort may provide a clearer picture of those at risk of developing progression and may capture additional patients at risk for poorer survival outcomes as a result.

While PD during NAC remains uncommon, its significant negative impact on DRFS demands this population be better understood. This study highlights that post-NAC tumor grade and T category are independent predictors of DRFS among patients with PD and may be utilized in the clinical setting as factors that heighten a provider's suspicion that a patient with PD and these features may experience a poorer overall outcome. As newer targeted systemic therapies

become available, the landscape of disease progression during NAC will continue to change, making it imperative that we continue to follow this population over time.

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