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Clinicopathological Factors That Predict Different Responses of Breast and Axillary Tumors to Neoadjuvant Chemotherapy and Prognosis Among Patients With Node-Positive Breast Cancer: Real World Data

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Keywords: breast cancer | neoadjuvant | node-positive | pathological complete response | prognosis

ABSTRACT

Background: Pathological complete response (pCR) has been proven to be related to prognosis. pCR can be further classified as pCR of the breast (bpCR), pCR of axillary lymph nodes (apCR) or pCR of both tumors. The aim of this study was to elucidate the outcomes and clinicopathological characteristics associated with different patterns of pCR.

Methods: Patients with node-positive disease who received neoadjuvant chemotherapy between August 2009 and July 2016 and who achieved pCR in axillary lymph nodes, breast or both were included. Multivariate logistic regression was used to identify factors related to different patterns of pCR.

Results: Among the 271 patients who were included in the study, 42.1% achieved total pCR, 46.1% achieved ApCR, and 11.8% achieved BpCR. Disease-free survival (DFS) was significantly better in the total pCR group than in the limited pCR groups throughout the entire cohort ($p = 0.042$). Univariate and multivariate analyses indicated that patients with HR-negative disease and a high Ki-67 proliferation index were more likely to achieve total pCR. Patients with earlier T stage disease were more likely to achieve pCR only in the breast. Among patients who achieved limited pCR, there was no significant difference in terms of whether these patients received intensified adjuvant chemotherapy.

Conclusions: Total pCR is still the best marker for predicting survival benefit in patients receiving neoadjuvant chemotherapy, and total pCR is more likely to be achieved in patients with HR-negative disease and a high Ki-67 proliferation index. T stage and N stage may predict apCR and bpCR, respectively.

1 | Introduction

Breast cancer has become the most frequently diagnosed cancer in the world [1]. Neoadjuvant chemotherapy (NACT) combined with subsequent surgical treatment has emerged as a well-recognized treatment strategy for locally advanced/node-positive breast cancer [2, 3]. Neoadjuvant chemotherapy can downstage the primary tumor and increase the breast

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conservation rate, and information about sensitivity to chemotherapy in vivo can guide subsequent adjuvant treatment.

Pathological complete response (pCR) refers to the absence of invasive disease in both the breast and axillary lymph nodes after NACT. Many studies have demonstrated a long-term prognostic benefit for patients who achieve pCR [4], and pCR is currently the gold standard for evaluating the efficacy of NACT. The pCR rate is influenced by several factors, such as hormone receptor (HR) status, human epidermal growth factor receptor 2 (HER2) status, clinical T stage, histological grade, and the Ki-67 proliferation index [5–9]. However, clinical pCR might be limited to either the breast or axilla; these conditions are called pCR of the breast (bpCR) or pCR of the axillary lymph nodes (apCR) instead of total pCR (tpCR), which is defined as pCR in both the breast and axillary lymph nodes. Few studies have investigated the role of adjuvant therapy in populations with limited pCR.

Therefore, in this study, we performed a real-world study in node-positive patients who received NACT to identify the differences between patients who achieved total pCR and those who achieved limited pCR, we explored the factors that predict total or limited pCR, and we analyzed the role of adjuvant therapy in the population of patients who achieve local pCR.

2 | Patients and Methods

The medical records of breast cancer patients who received NACT from August 2009 to July 2016 at the Cancer Hospital of the Chinese Academy of Medical Sciences were reviewed. The inclusion criteria were patients who were pathologically diagnosed with invasive breast cancer before NACT; whose clinical stage was $T_{1-4}N_{1-3}M_0$; and who achieved pCR in the breast, axillary lymph node or both. Patients were staged according to the eighth edition of the American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) classification [10]. Patients with distant metastasis, with missing stage information, or who underwent only local tumor resection were excluded.

All patients were diagnosed by core needle biopsy before the initiation of neoadjuvant treatment, and suspected axillary lymph nodes were assessed by fine needle biopsy or imaging. All patients received a standard NACT regimen as determined by a professional oncology team according to the guidelines for breast cancer published by the National Comprehensive Cancer Network (NCCN) and the China Anti-cancer Association Committee of Breast Cancer Society (CACA-CBCS). The following clinicopathological information was recorded: age, BMI, clinical N stage, clinical T stage, ER status, PR status, HER2 status, and Ki-67 proliferation index. The included patients were followed until December 2022, and follow-up information, including information on recurrence, metastasis, and death, was collected.

Pathology tumor specimens were evaluated by experts from the pathology department of Cancer Hospital, Chinese Academy of Medical Sciences, according to the guidelines of the American Society of Clinical Oncology/College of American Pathologists [11]. Estrogen and progesterone receptor positivity was defined as 1% or more of nuclei stained by immunohistochemistry. HER2 positivity was determined by immunohistochemical staining for HER2 (+++) and/or fluorescence in situ hybridization (FISH) for HER2 gene amplification [12]. Patients were subtyped according to ER, PR, and HER2 status. The classification of the HER2-positive population was based on the overexpression or gene amplification of HER2, regardless of the status of the hormone receptor. The HR+/HER2− group was defined as ER-positive and/or PR-positive with low expression or no amplification of HER2. The TNBC group was defined as being negative for hormone receptor and HER2 expression. High Ki-67 expression was defined by more than 20% nuclear staining.

2.1 | Definitions

pCR of the primary breast tumor was defined as the absence of residual invasive carcinoma in the excisional breast specimen, while pCR of the axillary lymph nodes was defined as the absence of measurable or metastatic disease in the excisional axillary lymph node specimen. Total pCR was defined as the absence of residual invasive carcinoma in both the breast and axillary lymph nodes. Anatomically limited pCR refers to pCR that is limited to only the breast or axillary lymph nodes.

2.2 | Statistical Analysis and Ethics

The Mann–Whitney *U* test was used to analyze differences in continuous variables (i.e., age, BMI), which are reported as median values with interquartile ranges (IQRs). Categorical variables were analyzed by the χ^2 test or Fisher's exact test, as appropriate. Survival was analyzed by the Kaplan–Meier method and comparisons between groups were performed with the log-rank test. Cox multiple factor regression analysis was used to analyze the independent influencing factors of DFS. All the factors with $p < 0.05$ in the univariate analysis were included in the multivariate logistic regression analysis to obtain the independent factors. All the analyses were conducted using SPSS statistics version 25.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 8 (GraphPad Software, San Diego, USA LCC). Differences were considered statistically significant at $p < 0.05$.

This study was approved by the Medical Center Institutional Review Board of the Cancer Hospital and Institute, Chinese Academy of Medical Sciences.

3 | Results

3.1 | Patient Characteristics

Among the 2140 patients who received NACT from August 2009 to July 2016, 271 patients who met the inclusion criteria were ultimately included in this study; of these patients, 114 achieved total pCR (42.1%), 125 achieved pCR only in the axillary lymph nodes (46.1%) and 32 achieved pCR only in the breast (11.8%). In the total pCR population, the proportion of HR+/HER2− patients was the lowest (17.5%), and the proportion of patients with the HER2-positive subtype was the highest (58.8%). The same trend was observed for the apCR and bpCR populations. Of the

TABLE 1 | Patient characteristics.

	All patients	Response to NACT		
		Total pCR	Axillary pCR	Breast pCR
	N = 271	*N* = 114 (42.1%)	*N* = 125 (46.1%)	*N* = 32 (11.8%)
Age, years—median (IQR)	48.0 (42.0–55.0)	50.0 (42.0–56.3)	47.0 (41.0–55.0)	47.5 (40.8–54.0)
BMI, kg/m^2—median (IQR)	25.0 (23.0–27.2)	24.5 (22.3–27.1)	25.3 (23.4–27.3)	25.3 (23.9–26.5)
Clinical T stage				
cT1	19 (7.0)	10 (8.8)	3 (2.4)	6 (18.8)
cT2	167 (61.6)	68 (59.6)	78 (62.4)	21 (65.6)
cT3	31 (11.4)	16 (14.0)	15 (12.0)	0 (0.0)
cT4	54 (19.9)	20 (17.5)	29 (23.2)	5 (15.6)
Clinical N stage				
cN1	119 (43.9)	48 (42.1)	64 (51.2)	7 (21.9)
cN2	107 (39.5)	44 (38.6)	46 (36.8)	17 (53.1)
cN3	45 (16.6)	22 (19.3)	15 (12.0)	8 (25.0)
ER status				
Negative	162 (59.8)	82 (71.9)	63 (50.4)	17 (53.1)
Positive	109 (40.2)	32 (28.1)	62 (49.6)	15 (46.9)
PR status				
Negative	147 (54.2)	70 (61.4)	63 (50.4)	14 (43.8)
Positive	124 (45.8)	44 (38.6)	62 (49.6)	18 (56.3)
HER2 status				
Negative	116 (42.8)	45 (39.5)	58 (46.4)	13 (40.6)
Positive	144 (53.1)	67 (58.8)	59 (47.2)	18 (56.3)
Unknown	11 (4.1)	2 (1.8)	8 (6.4)	1 (3.1)
Ki-67 status				
Low	44 (16.2)	10 (8.8)	28 (22.4)	6 (18.8)
High	211 (77.9)	94 (82.5)	94 (75.2)	23 (71.9)
Unknown	16 (5.9)	10 (8.8)	3 (2.4)	3 (9.4)
Molecular subtypes				
HER2+	144 (53.1)	67 (58.8)	59 (47.2)	18 (56.3)
HR+/HER2−	61 (22.5)	20 (17.5)	32 (25.6)	9 (28.1)
TNBC	55 (20.3)	25 (21.9)	26 (20.8)	4 (12.5)
HER2 unknown	11 (4.1)	2 (1.8)	8 (6.4)	1 (3.1)
Chemotherapy regimen				
Taxane-based	107 (39.5)	54 (47.4)	43 (34.4)	10 (31.3)
Anthracycline-taxane combination	161 (59.4)	58 (50.9)	81 (64.8)	22 (68.8)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; PR, progesterone receptor.

enrolled patients, 161 (59.4%) received anthracycline-taxane combination therapy, while 107 (39.5%) were treated with taxane-based regimens excluding anthracyclines. Notably, triple-negative breast cancer patients predominantly received either anthracycline-taxane combinations or paclitaxel-platinum regimens. Among HER2-positive patients, the majority were treated with anthracycline-taxane combination or taxane-carboplatin-trastuzumab combinations. Targeted therapy was administered

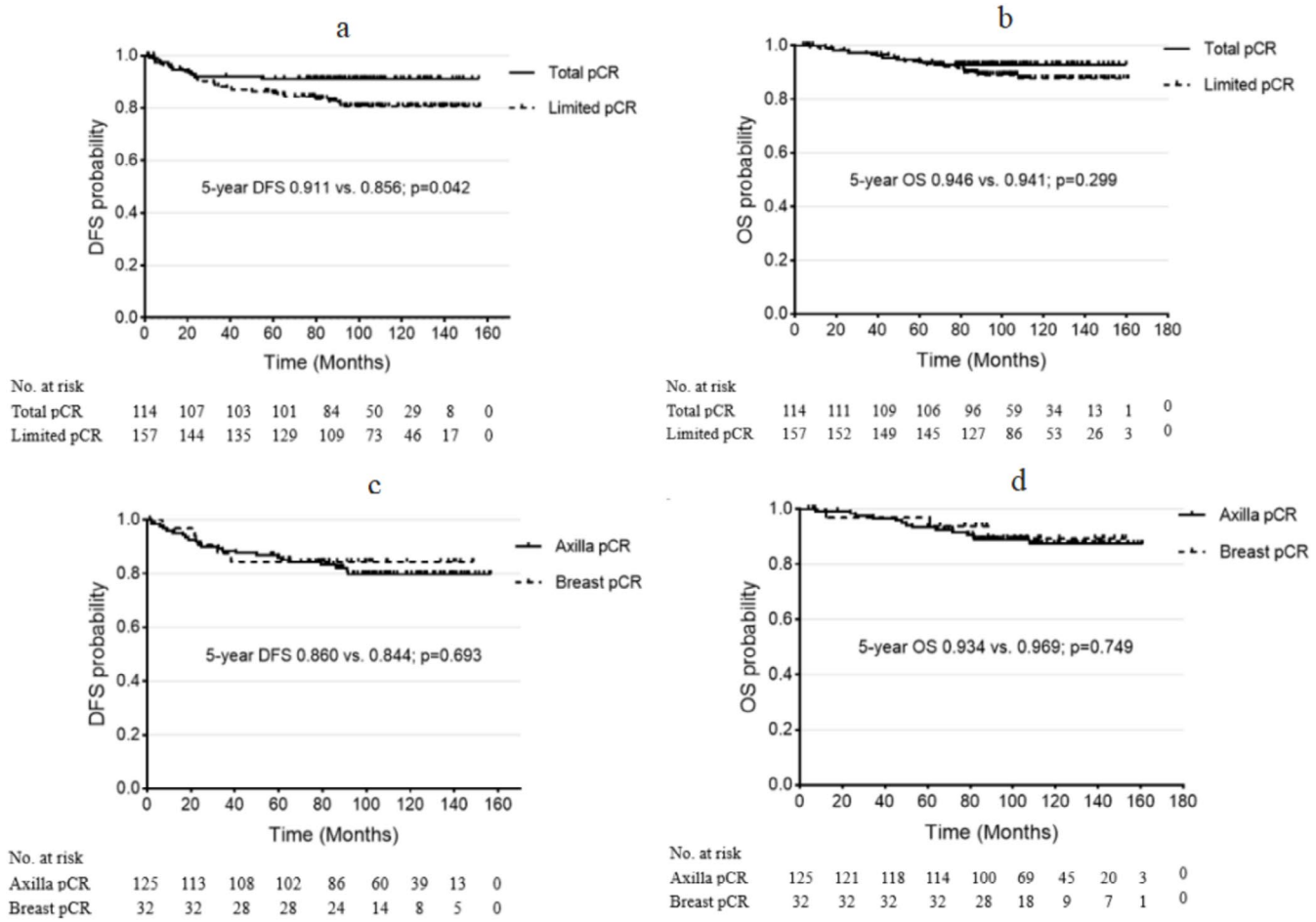

FIGURE 1 | Survival curves of the patients. (a) DFS of patients with total pCR and pCR anatomically limited to the breast or axillary lymph nodes. (b) OS of patients with total pCR and pCR anatomically limited to the breast or axillary lymph nodes. (c) DFS of patients with pCR limited to the breast and axillary lymph nodes. (d) OS of patients with pCR limited to the breast and axillary lymph nodes.

TABLE 2 | Multivariate analysis for disease-free survival.

Factors	Hazard ratio	95% CI	*p*
Clinical N stage			
cN1–2	0.392	0.194–0.792	0.009
cN3	Ref.		
Response			
Total pCR	0.454	0.220–0.937	0.033
Limited pCR	Ref.		

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; pCR, pathological complete response.

to 67 (46.5%) HER2-positive patients, primarily involving trastuzumab-based regimens. Other clinical and pathological characteristics are summarized in Table 1.

3.2 | Survival

Among the 271 patients who were included, 34 had recurrence and/or metastasis, and 22 died before December 31, 2022. The median follow-up time was 102.1 months. The 5-year DFS of patients who achieved total pCR after NACT was significantly better than that in patients who achieved a pCR only in the axillary lymph node or breast (5-year DFS, 0.911 vs. 0.856; $p = 0.042$) (Figure 1a). The 5-year OS in the tpCR group was better than that in the limited pCR group, but the difference was not statistically significant (5-year OS, 0.946 vs. 0.941; $p = 0.299$) (Figure 1b). No significant differences were observed in either 5-year DFS (5-year DFS, 0.860 vs. 0.844; $p = 0.693$) or 5-year OS (5-year OS, 0.934 vs. 0.969; $p = 0.749$) between patients who achieved pCR only in the axillary lymph nodes and those who achieved pCR only in the breast (Figure 1c,d).

The clinicopathological factors with p values lower than 0.05 in the univariate Cox regression analysis were included in the multivariate analysis (Table 2). The results showed that early clinical N stage (HR, 0.392; 95% CI, 0.194–0.792; $p = 0.009$) and total pCR (HR, 0.454; 95% CI, 0.220–0.937; $p = 0.033$) were independent influencing factors for better DFS.

Survival analysis was also performed separately for patients with different molecular subtypes. Among HER2-positive patients, those who achieved total pCR after NACT had a better DFS than those who achieved pCR limited to the axillary lymph node or breast, but this difference was not statistically significant (HR, 0.48; 95% CI, 0.21–1.09; $p = 0.097$) (Figure 2a). Among

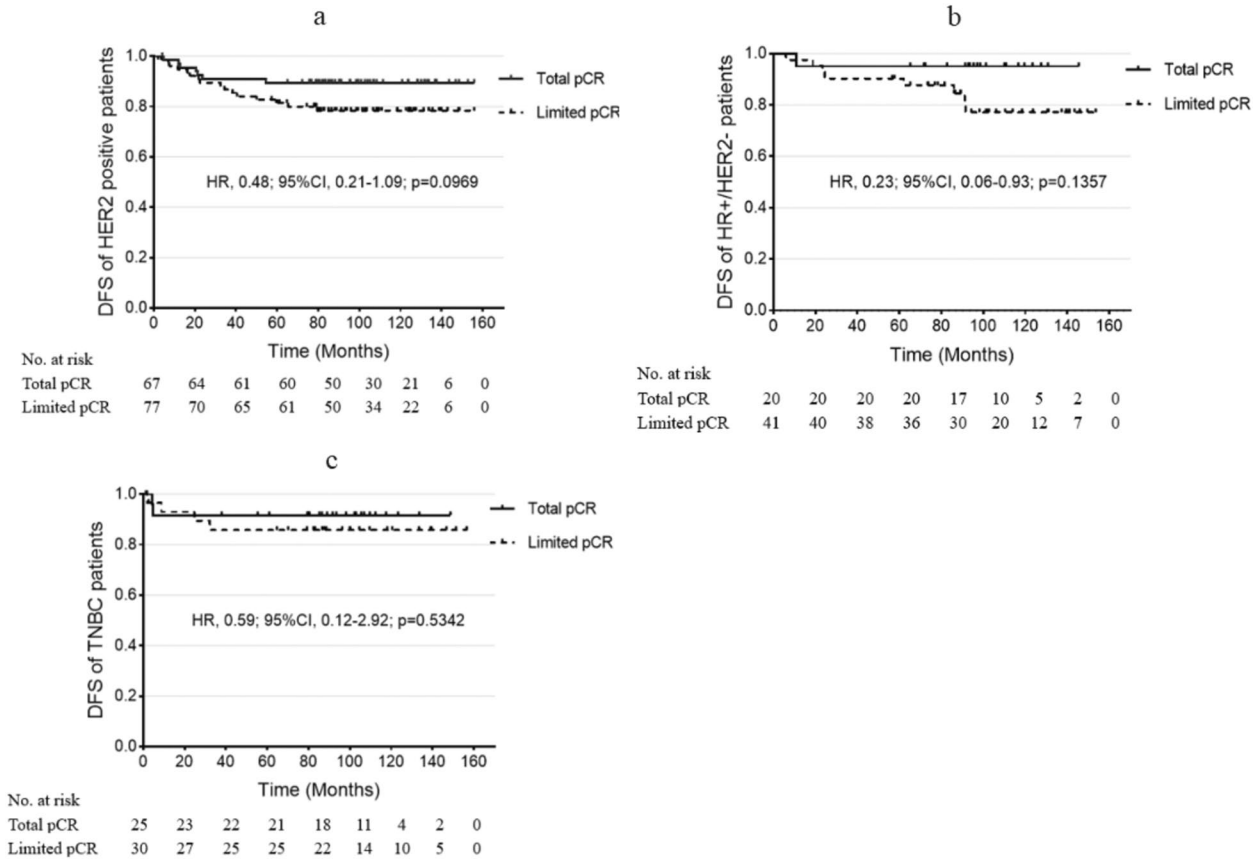

FIGURE 2 | Survival curves of patients with different subtypes. (a) DFS of HER2-positive patients with total pCR and pCR anatomically limited to the breast or axillary lymph nodes. (b) DFS of HR+/HER2− patients with total pCR and pCR anatomically limited to the breast or axillary lymph nodes. (c) DFS of TN patients with total pCR and pCR anatomically limited to the breast or axillary lymph nodes.

HR+/HER2− and TNBC patients, the DFS of patients who achieved total pCR after NACT was better than that of patients who achieved limited pCR, but the differences were not statistically significant (Figure 2b,c).

3.3 | Characteristics Associated With pCR Patterns

3.3.1 | Overall pCR Versus Anatomically Limited pCR

We evaluated the differences in clinical and histological characteristics between patients who achieved total pCR and those who achieved anatomically limited pCR (Table 3). According to the univariate analysis, the total pCR group had a significantly higher proportion of patients with HR-negative disease ($p=0.015$) and a high Ki-67 proliferation index ($p=0.007$). Factors with p values less than 0.05 in the univariate analysis were then included in the multivariate logistic regression analysis. The final results suggested that patients with HR-negative disease (OR = 1.944; 95% CI, 1.161–3.256; $p=0.011$) or a high Ki-67 proliferation index (OR = 0.384; 95% CI, 0.179–0.824; $p=0.014$) were more likely to achieve total pCR (Table 3).

3.3.2 | Axillary pCR Versus Breast pCR

According to the univariate analysis, there was a significant difference in clinical T stage ($p=0.002$) between the two groups. Compared with patients who achieved breast pCR, patients who achieved axillary pCR had earlier clinical N stage disease ($p=0.009$). Furthermore, we performed a multivariate analysis using these factors. Patients with early clinical T stage disease (OR = 0.127; 95% CI 0.028–0.572; $p=0.002$) at diagnosis were significantly more likely to achieve pCR only in the breast. Conversely, patients with cN1 (OR = 4.109; 95% CI 1.225–13.782; $p=0.022$) were more likely to achieve pCR only in the axillary lymph nodes (Table 4).

3.4 | Intensive Adjuvant Therapy for Patients With Limited pCR

Postoperative treatment information was collected for 136 of the 157 patients who achieved limited pCR in this study; this group included 23 patients who received intensive adjuvant therapy (16.9%), 22 patients (20.2%) in the axillary pCR group and 1 patient (3.7%) in the breast pCR group. Patients who received intensive adjuvant therapy were all treated with chemotherapy as the adjuvant therapy regimen, including paclitaxel combined with carboplatin or paclitaxel combined with cyclophosphamide. Among the 23 patients who received intensive adjuvant therapy, 21.7% had HER2-positive disease, 47.8% had HR+/HER2− disease, 26.1% had triple-negative disease, and 4.3% had an unknown HER2 status.

To reduce the effects of clinical N stage, subtype, and response to NACT, patients who were not treated with intensive adjuvant

TABLE 3 | Predictors of total pCR.

	All patients	Response to NACT				
		Total pCR	Limited pCR		Odds ratio (95% CI)	
	N = 271	*N* = 114 (43.5%)	*N* = 157 (56.5%)	*p*		*p*
Age, years—median (IQR)	48.0 (42.0–55.0)	50.0 (42.0–56.3)	47.0 (41.0–55.0)	0.448		
BMI, kg/m^2—median (IQR)	25.0 (23.0–27.2)	24.5 (22.3–27.1)	25.3 (23.6–27.3)	0.097		
Clinical T stage				0.333		
cT1	19 (7.0)	10 (8.8)	9 (5.7)			
cT2–4	252 (93.0)	104 (91.2)	148 (94.3)			
Clinical N stage				0.593		
cN1	119 (43.9)	48 (42.1)	71 (45.2)			
cN2	107 (39.5)	44 (38.6)	63 (40.1)			
cN3	45 (16.6)	22 (19.3)	23 (14.6)			
HR status				0.015		
Negative	117 (43.2)	59 (51.8)	58 (36.9)		1.944 (1.161–3.256)	0.011
Positive	154 (56.8)	55 (48.2)	99 (63.1)		Ref.	
HER2 status				0.211		
Negative	116 (44.6)	45 (40.2)	71 (48.0)			
Positive	144 (55.4)	67 (59.8)	77 (52.0)			
Ki-67				0.007		
Low	44 (17.3)	10 (9.6)	34 (22.5)		0.384 (0.179–0.824)	0.014
High	211 (82.7)	94 (90.4)	117 (77.5)		Ref.	

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; limited pCR, pCR anatomically limited to the breast or axillary lymph node; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; PR, progesterone receptor.

therapy were matched with those in the intensive adjuvant therapy group according to 1:1 propensity score matching (PSM) with a caliper value of 0.02. Among patients who achieved limited pCR, survival analysis revealed no significant differences in DFS or OS between those who received intensive adjuvant therapy and those who did not receive intensive adjuvant therapy (Figure 3a,b).

4 | Discussion

A pCR is the most ideal response to NACT [13]. The prognostic value of pCR is notable in patients with HER2-positive and TNBC disease, and patients who do not achieve pCR can benefit from postoperative treatment with trastuzumab, emtansine, and capecitabine [14, 15]. It is very important to identify the factors that are associated with different patterns of pCR, so we can identify patients who might not need to undergo mastectomy or lymph node dissection and who might need treatment consolidation. In our study, we found that patients who achieved limited pCR had comparable OS but worse DFS than those who achieved total pCR.

In Fayanju's study, the OS rates of patients with total pCR, pCR only in the breast and pCR only in the axillary lymph nodes were 94%, 83%, and 85%, respectively, which indicated that limited pCR predicts worse prognosis compared with overall pCR [13]. However, there are still many different conclusions at present [16]. In our study, we found that OS was not significantly different between the total and limited pCR groups (96.9% vs. 93.4%). The reasons for the inconsistency were as follows. First, Fayanju's study was based on the National Cancer Database (NCDB), and our research included Chinese patients. Second, the sample size of our study was limited. Third, more HER2-positive patients were enrolled in our study, which might influence the survival rate. Additionally, Fayanju's study suggested that patients can benefit from improvements in total or limited pCR.

ER and PR are gene regulatory proteins that work together to directly regulate the epidermal growth factor receptor pathway and subsequently affect mammary epithelial cell growth, differentiation, and survival. Some studies have shown that ER-positive tumors respond better to chemotherapy [9], while others believe that ER can mediate chemoresistance [17, 18]. In

TABLE 4 | Predictors of pCR only in the breast.

	All patients	Response to NACT				
		Axillary pCR	Breast pCR			
	N = 157	*N* = 125 (79.7%)	*N* = 32 (20.3%)	*p*	Odds ratio (95% CI)	*p*
Age, years—median (IQR)	47.0 (41.0–55.0)	47.0 (41.0–55.0)	47.5 (40.8–54.0)	0.663		
BMI, kg/m^2—median (IQR)	25.3 (23.6–27.3)	25.3 (23.4–27.3)	25.3 (23.9–26.5)	0.910		
Clinical T stage				0.002		
cT1	9 (5.7)	3 (2.4)	6 (18.8)		0.127 (0.028–0.572)	0.007
cT2–4	148 (94.3)	112 (97.6)	26 (81.3)		Ref.	
Clinical N stage				0.009		
cN1	71 (45.2)	64 (51.2)	7 (21.9)		4.109 (1.225–13.782)	0.022
cN2	63 (40.1)	46 (36.8)	17 (53.1)		1.270 (0.431–3.741)	0.664
cN3	23 (14.6)	15 (12.0)	8 (25.0)		Ref.	
HR status				0.736		
Negative	58 (36.9)	47 (37.6)	11 (34.4)			
Positive	99 (63.1)	78 (62.4)	21 (65.5)			
HER2 status				0.449		
Negative	71 (48.0)	58 (49.6)	13 (41.9)			
Positive	77 (52.0)	59 (50.4)	18 (58.1)			
Ki-67				0.793		
Low	34 (22.5)	28 (23.0)	6 (20.7)			
High	117 (77.5)	94 (77.0)	23 (79.3)			

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; limited pCR, pCR anatomically limited to the breast or axillary lymph nodes; NACT, neoadjuvant chemotherapy; pCR, pathological complete response.

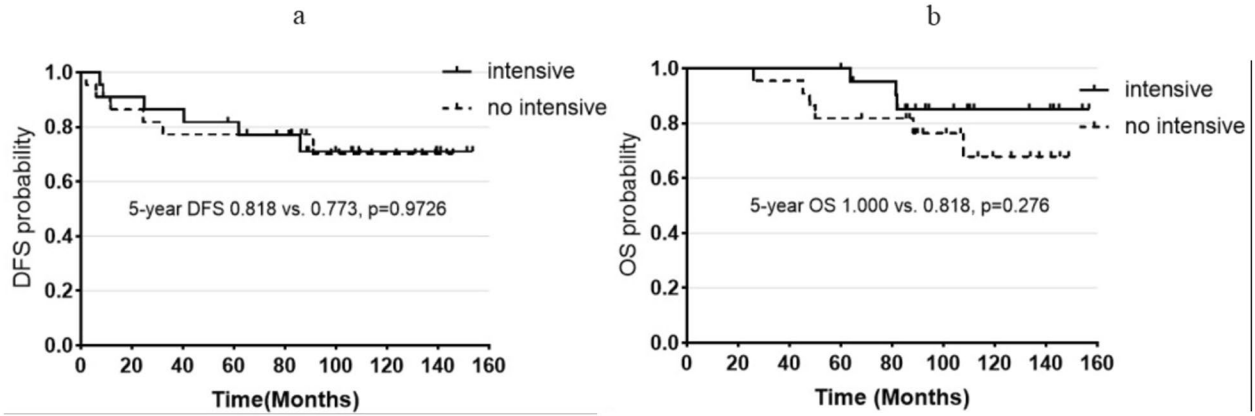

FIGURE 3 | Survival curves of patients who did and did not receive intensive adjuvant therapy. (a) DFS of patients who did and did not receive intensive adjuvant therapy. (b) OS of patients who did and did not receive intensive adjuvant therapy.

one study, ER-positive human breast cancer cells were transfected with estrogen receptor alpha, and the results indicated that ER may be involved in mediating resistance to chemotherapy through the inhibition of drug-induced apoptotic cell death [19]. A clinical study suggested that ER-negative tumors showed an increased pathological response to chemotherapy, and ER status seems to be more sensitive than PR status in predicting the pathological response to preoperative chemotherapy. Due to the correlation between ER and PR, we combined them into HR for analysis. HR-negative patients were more likely to achieve total pCR than patients with anatomically limited pCR, which is consistent with previous studies. Indeed, in clinical practice, it is

not difficult to observe that HER2-positive patients with HR-negative status achieve significantly higher pCR rates with neoadjuvant therapy compared to HER2-positive patients with HR-positive status [20]. This result may suggest that HR-positive patients or those with low Ki-67 expression are less responsive to NACT and may require an escalation of their treatment regimen or extended chemotherapy duration.

Ki67 is a nuclear protein, and its expression level often reflects cell proliferation. Several studies have suggested that Ki-67 may be associated with chemotherapy response and prognosis in patients with breast cancer [21, 22]. At present, a number of meta-analyses have shown that among breast cancer patients who receive NACT, the pCR rate of patients with a high Ki-67 proliferation index is significantly higher than that of patients with a low Ki-67 proliferation index, but the cutoff values of the Ki-67 index are different in various studies, ranging from 10% to 50% [5, 23]. In this study, 20% was chosen as the Ki-67 threshold [24]. The results suggested that in the general population, a high Ki-67 index was an independent predictor of total pCR. In the HER2-positive population, Ki-67 was significantly different between patients with total and anatomically limited pCR, but it was not an independent predictor of total pCR.

By comparing data from patients with pCR only in the breast versus patients with pCR only in the axillary lymph nodes, we found that patients with cN1 were more likely to achieve pCR only in the axillary lymph nodes, while patients with cT1 were more likely to achieve pCR only in the breast, which is consistent with the results of previous studies [25, 26]. We therefore speculate that clinical T stage and clinical N stage may be factors that lead to inconsistent responses between the breast and the axilla. However, in the HER2-positive population, only the clinical N stage was significantly different between patients who achieved pCR only in the axillary lymph nodes and those who achieved pCR only in the breast. This may be related to the administration of neoadjuvant targeted therapy.

According to previous studies, the prognosis of patients with limited pCR is worse than that of patients with total pCR. The KATHERINE study revealed that for patients who did not achieve pCR after NACT, intensified adjuvant therapy with trastuzumab emtansine can significantly improve DFS [14]. The results of the CREATE-X study showed that in patients with HER2-negative (especially triple-negative) residual invasive breast cancer after NACT, receiving standard postsurgical treatment with capecitabine can significantly improve DFS and OS [15]. In this study, only 16.9% of patients received intensive adjuvant therapy. Survival analysis revealed no significant difference between patients who received and did not receive intensive adjuvant therapy. The reason for this result may be that the enrolled patients received treatment in the early years, and molecular-based intensified adjuvant reinforcement has not yet been widely implemented in clinical practice. In addition, the small number of enrolled patients may also cause bias in the results. This study represents a breakthrough in comparing patients who achieved total pCR, pCR of the breast, and pCR of the axillary lymph nodes after neoadjuvant therapy to explore differences in prognosis and clinicopathological factors. However, our study was only a single-center retrospective study with a relatively small number of patients. Selection bias and recall bias during data collection may be unavoidable. Further validation of these findings in larger-scale multicenter studies is necessary. Moreover, approximately 10.7% of the patients in this study were lost to follow-up, which may have affected the results of the survival analysis. A systematic review could avoid this problem.

Previous studies have revealed many indicators related to the efficacy of NACT for treating breast cancer, including not only clinical pathological factors but also immune-related indicators, circulating tumor indicators, imaging indicators, and so on [27–31]. It is expected that more large-scale studies can include these indicators, explore their relationships with overall and anatomically limited pCR, and establish a more comprehensive, accurate, and practical predictive model of NACT for breast cancer. The results can hopefully provide a basis for the selection of potential candidates for clinical trials. In addition, our study can help clinicians in making decisions when treating patients who are receiving NACT.

5 | Conclusion

By comparing patients who achieved total pCR and patients who achieved limited pCR, we found that total pCR can lead to better DFS, and this survival benefit may vary with molecular subtype. We demonstrated that patients with HR-negative disease and a high Ki-67 proliferation index are more likely to achieve total pCR than patients who achieve anatomically limited pCR. Moreover, clinical T stage and clinical N stage may be factors that lead to inconsistent responses between the breast and the axilla. Subtype-based intensive adjuvant therapy is necessary. However, further studies are needed to validate these results in clinical practice.

Author Contributions

All authors contributed to the study conception and design. Danyang Ji and Bo Lan: manuscript writing, data collection and analysis, manuscript writing. Jiayu Wang, Fei Ma, Yang Luo, Qing Li, Pin Zhang, Ruigang Cai, Qiao Li, and Shanshan Chen: management of patients and data collection. Binghe Xu and Ying Fan: study design and supervision. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors have approved the final version of the manuscript for submission.

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Disclosure

The authors have nothing to report.

Ethics Statement

The study was approved by the ethics committee of Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College

and all other participating centers. All patients provided written informed consent.

Consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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