Clinical N3 is an independent risk factor of recurrence for breast cancer patients achieving pathological complete response and near-pathological complete response after neoadjuvant chemotherapy

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Abstract

Background: Although achieving pathological complete response (pCR) and near-pathological complete response (near-pCR) after neoadjuvant chemotherapy (NAC) in breast cancer predicts a better outcome, some patients still experience recurrence. The aim of our study was to analyse the predictive factors of recurrence in the pCR and near-pCR population.

Methods: We reviewed 1209 breast cancer patients treated with NAC. A total of 292 patients achieving pCR and near-pCR between January 2010 and April 2021 in the Cancer Hospital, Chinese Academy of Medical Sciences (CHCAMS) were included in our analysis. pCR was defined as ypT0N0/ypTisN0. Near-pCR was defined as ypT1mi/1a/1bN0 or ypT0/isN1mi. The Kaplan-Meier method with the log rank test was used to estimate recurrence analysis.

Results: Of the 292 patients,173 were pCR and 119 were near-pCR. The median age was 46 years (range 23-75 years). The predominant tumor subtype was human epidermal growth factor receptor type 2 (HER2) positive (49.0%) and triple-negative breast cancer (TNBC) (30.8%). The median duration of follow-up was 53 months (range 9-138 months). A total of 16 (8.9%) patients developed recurrence, with 9 (5.2%) in the pCR group and 16 (13.4%) in the near-pCR group. The vast majority of recurrence occurred within 36 months from onset of NAC. The 5-year recurrence-free survival (RFS) rate of patients achieving pCR was significantly higher than that of patients achieving near-pCR (94.6% vs.85.6%, P=0.008). Clinical N3 (cN3) before NAC was an independent factor of higher risk for recurrence in patients who achieved pCR (P=0.003) and near-pCR (P=0.036). Tumor size before NAC, subtype of breast cancer and chemotherapy regimens showed no significant association with RFS both for patients who achieved pCR and near-pCR ($P \geq 0.05$).

Conclusions: cN3 before NAC was an independent factor of higher risk for recurrence in patients who achieved pCR and near-pCR. It is worthwhile to monitor closely for patients with cN3, especially in the first 3 years.

Background

Neoadjuvant chemotherapy (NAC) was widely used in patients with human epidermal growth receptor 2 (HER2) positive and triple negative breast cancer (TNBC) [1–3]. HER2-positive breast cancer and TNBC are relatively sensitive to NAC and pathological reaction to NAC can provide prognostic information and guide the selection of postoperative treatment [4–9]. Due to the rapid development of antineoplastic drugs in recent decades, the rate of pathological complete response (pCR) after NAC has significantly increased[10]. Studies have demonstrated that patients achieving pCR had significantly better disease-free survival (DFS) and overall survival (OS) than patients with residual disease[11, 12]. More recently, the concept of near-pCR was gradually being proposed and attracted more and more attention. Substantial researches elucidated that patients who achieved near-pCR also had outstanding DFS and OS[13, 14].

In spite of the outstanding prognosis of patients achieving pCR and near-pCR, some of them may still experience recurrence. In order to identify clinical and pathological predictors of cancer relapse, we performed this retrospective analysis among breast cancer patients who achieved pCR and near-pCR in the Cancer Hospital, Chinese Academy of Medical Sciences (CHCAMS). In this study, we aimed to explore the predictive factors associated with recurrence for the patients achieving pCR and near-pCR, and investigate whether the risk for recurrence and death of patients achieving near-pCR after NAC was comparable with those achieving pCR.

Methods

1.1 Study population

We reviewed 1209 breast cancer patients that were treated with NAC and received surgery afterward between January 2010 and April 2021 in CHCAMS. Patients with distant metastasis during NAC, without detailed pathology after surgery and withdraw active follow up data were excluded. A final cohort of 292 patients who achieved pCR and near-pCR was incorporated in this study. Clinical and pathological data of these patients were collected, including age, menstruation, tumor size, regional lymph node, estrogen receptor (ER), progesterone receptor (PR), HER2, Ki67 index, chemotherapy, radiation, endocrine, and surgery regimen.

1.2 Pathological assessment

pCR was defined as no residual invasive carcinoma in the breast and negative axillary lymph nodes, including ypT0N0 and ypTisN0. Near-pCR was defined as the residual tumor size ≤ 1cm in the breast and negative axillary lymph nodes, or no residual invasive carcinoma in the breast yet existing micrometastasis in lymph node, including ypT1mi/a/bN0 and ypT0/isN1mi.

The Miller-Payne grade system was used to evaluate breast cancer pathological responses to NAC. Grade 1: no significant reduction in tumour cells; Grade 2: a minor reduction in tumour cells (≤ 30%); Grade 3: reduction in tumour cells between 30% and 90%; Grade 4: disappearance of tumour cells > 90%; Grade 5: no invasive tumor cells identifiable, DCIS may be present.

ER and PR status was assessed by immunohistochemistry (IHC) and categorized as positive when more than 1% of cancer cells were stained. HER2 positivity was defined as 3 + by IHC or positive by fluorescence in situ hybridization (FISH).

Recurrence-free survival (RFS) was calculated as the time from the onset of NAC to locally or distant recurrence, or death due to breast cancer, whichever came first. Overall survival (OS) was calculated as the time from the onset of NAC to death due to any cause.

1.3 Statistical analysis

All statistical analyses were conducted using SPSS 25.0 and R (version 3.5.1). The Kaplan-Meier method with the log-rank test was used for recurrence and survival analysis. Group comparisons for categorical variables were carried out using Fisher's exact test. The factors significant at the 20% level in the univariate analysis were considered for inclusion in the multivariate model. The cox proportional hazards regression model was used to assess the association of clinical and pathological predictors with RFS. All tests were two tailed and a *P*-value less than 0.05 was considered to indicate a statistically significant difference.

Results

1.1 Patient characteristics

A total of 292 patients with pCR and near-pCR were included in this study. Their clinical and pathological characteristics are described in the Table 1. The median age of patients was 46 years (range 23–75 years). 62.3% were premenopausal. The median duration of follow-up for these patients was 53 months (range 9-138 months). There were 173 patients achieving pCR and 119 achieving near-pCR. The predominant tumor subtype was HER2 positive (49.0%) (including luminal B HER2 + and non-luminal HER2+) and TNBC (30.8%). Among the patients with HER2 positive, 63.6% received trastuzumab, while 24.4% received trastuzumab and pertuzumab. The majority of the tumors were T2+ (91.4%) and N+ (76.0%). Overall, 77.0% of the patients underwent mastectomy and 83.2% of the patients had axillary lymph node dissection.

Table 1
Patient characteristics

Characteristics	Total (n = 292)		pCR (n = 173)		Near-pCR (n = 119)	
	No.	%	No.	%	No.	%
Median age (range)	46(23–75)		48(23–73)		42(24–75)	
Age						
40	94	32.2	43	24.9	51	42.9
40–59	168	57.5	110	63.6	58	48.7
≥ 60	30	10.3	20	11.6	10	8.4
Menopausal status						
Premenopausal	182	62.3	101	58.4	81	68.1
Postmenopausal	110	37.7	72	41.6	38	31.9
cT						
T1	25	8.6	15	8.7	10	8.4
T2	168	57.5	108	62.4	60	50.4
T3	69	23.6	35	20.2	34	28.6
T4	30	10.3	15	8.7	15	12.6
cN						
N0	70	24.0	33	19.1	37	31.1
N1	69	23.6	35	20.2	34	28.6
N2	98	33.6	68	39.3	30	25.2
N3	55	18.8	37	21.4	18	15.1
cTNM						
I	4	1.4	1	0.6	3	2.5
IIA	49	16.8	23	13.3	26	21.8
IIB	51	17.5	29	16.8	22	18.5

Abbreviation:pCR:pathological complete response;Near-pCR:near-pathological complete response; cT:clinical tumour size; cN: clinical lymph node status;ER: estrogen receptor; PR: progesterone receptor; HER2:human epidermal growth factor receptor type 2; Ki67:Ki67 index; NAC:neoadjuvant chemotherapy; TKI:Tyrosine Kinase Inhibitor.

Characteristics	Total (n = 292)		pCR (n = 173)		Near-pCR (n = 119)	
	No.	%	No.	%	No.	%
IIIA	108	37.0	70	40.5	38	31.9
IIIB	25	8.6	13	7.5	12	10.1
IIIC	55	18.8	37	21.4	18	15.1
ER status						
Negative	203	69.5	128	74.0	75	63.0
Positive	89	30.5	45	26.0	44	37.0
PR status						
Negative	174	59.6	115	66.5	59	49.6
Positive	118	40.4	58	33.5	60	50.4
HER2 status						
Negative	149	51.0	86	49.7	63	52.9
Positive	143	49.0	87	50.3	56	47.1
Ki67						
20	16	5.5	7	4.0	9	7.6
20–49	117	40.1	65	37.6	52	43.7
≥ 50	142	48.6	92	53.2	50	42.0
Unknown	17	5.8	9	5.2	8	6.7
Breast cancer subtype						
Luminal A	1	0.3	0	0.0	1	0.8
Luminal B HER2-	58	19.9	30	17.3	29	24.4
Luminal B HER2+	77	26.4	41	23.7	35	29.4
Non-luminal HER2+	66	22.6	45	26.0	21	17.6
Triple negative	90	30.8	57	32.9	33	27.7
Chemotherapy regimens of NAC						

Abbreviation:pCR:pathological complete response;Near-pCR:near-pathological complete response; cT:clinical tumour size; cN: clinical lymph node status;ER: estrogen receptor; PR: progesterone receptor; HER2:human epidermal growth factor receptor type 2; Ki67:Ki67 index; NAC:neoadjuvant chemotherapy; TKI:Tyrosine Kinase Inhibitor.

Characteristics	Total (n = 292)		pCR (n = 173)		Near-pCR (n = 119)	
	No.	%	No.	%	No.	%
Anthracycline and taxane	86	29.5	40	23.1	46	38.7
Taxane and platinum	175	59.9	117	67.6	58	48.7
Anthracycline and taxane and platinum	15	5.1	10	5.8	5	4.2
Anthracycline or taxane	13	4.5	6	3.5	7	5.9
Endocrine	3	1.0	0	0.0	3	2.5
Cycle number of NAC						
≤4	10	3.4	2	1.2	8	6.7
4–6	248	84.9	153	88.4	95	79.8
≥6	31	10.6	18	10.4	13	10.9
Other (Endocrine Therapy)	3	1.0	0	0.0	3	2.5
Surgery of breast cancer						
Breast-conserving surgery	67	23.0	41	23.7	26	21.8
Mastectomy	225	77.0	132	76.3	93	78.2
Surgery of lymph nodes						
Sentinel lymph node biopsies	49	16.8	28	16.2	21	17.6
Axillary lymph node dissection	143	83.2	145	83.8	98	82.4
Adjuvant radiation						
Yes	211	72.3	125	72.3	86	72.3
No	81	27.7	48	27.7	33	27.7
Adjuvant endocrine						
Yes	128	43.8	67	38.7	61	51.3
No	164	56.2	106	61.3	58	48.7
HER2 positive						

Abbreviation:pCR:pathological complete response;Near-pCR:near-pathological complete response; cT:clinical tumour size; cN: clinical lymph node status;ER: estrogen receptor; PR: progesterone receptor; HER2:human epidermal growth factor receptor type 2; Ki67:Ki67 index; NAC:neoadjuvant chemotherapy; TKI:Tyrosine Kinase Inhibitor.

Characteristics	Total (n = 292)		pCR (n = 173)		Near-pCR (n = 119)	
	No.	%	No.	%	No.	%
With trastuzumab	91	63.6	59	67.8	32	57.1
With trastuzumab and pertuzumab	35	24.4	23	26.4	12	21.4
With trastuzumab and TKI	1	0.7	0	0	1	1.8
Without HER2 targeted therapy	16	11.1	5	5.7	11	19.6

Abbreviation:pCR:pathological complete response;Near-pCR:near-pathological complete response; cT:clinical tumour size; cN: clinical lymph node status;ER: estrogen receptor; PR: progesterone receptor; HER2:human epidermal growth factor receptor type 2; Ki67:Ki67 index; NAC:neoadjuvant chemotherapy; TKI:Tyrosine Kinase Inhibitor.

1.2 Disease recurrence

As shown in Table 2, a total of 26 (8.9%) patients developed recurrence. Twenty-one (84.0%) recurrence occurred within 36 months. Among patients achieving pCR, 9 (5.2%) patients developed cancer recurrence, with 2 patients presenting with both local relapse and distant metastasis, while 7 patients presenting with distant metastasis. The median time to recurrence was 14 months (range, 8–62 months) from the onset of NAC. 4 (44.4%) patients occurred liver metastasis and 2 (22.2%) patients presented brain metastasis as the first event.

Table 2
Time and site of recurrence

	pCR		Near-pCR	
	N	%	N	%
	9		16	
Median (range), months	14 (8–62)		18(4–69)	
≤ 12 months	3	33.3	5	31.3
12–36 months	4	44.4	9	56.3
36 months	2	22.2	2	12.5
Site of disease recurrence				
local recurrence	2	22.2	8	50
breast or chest wall	1	11.1	3	18.8
regional lymph nodes	1	11.1	5	31.3
distant metastasis	9	100	12	75
liver	4	44.4	1	6.3
lung	1	11.1	3	18.8
brain	2	22.2	2	12.5
bone	0	0	6	37.5
Other sites	2	22.2	2	12.5
Abbreviation:pCR:pathological complete response;Near-pCR:near-pathological complete response.				

Regarding patients achieving near-pCR, 16 (13.4%) patients developed cancer recurrence, with 4 patients presenting with local relapse only, 4 patients with both local relapse and distant metastasis, while 8 patients presenting with distant metastasis only. The median time to recurrence was 18 months (range, 4–69 months). Three (18.8%) patients experienced lung metastasis and 6 (37.5%) patients presented bone metastasis as the first event.

1.3 RFS and OS

The 3-year RFS rates of patients achieving pCR and near-pCR were 95.6% and 85.6%, respectively. The 5-year RFS rates of patients achieving pCR and near-pCR were 94.6% and 85.6%, respectively. The risk of cancer recurrence was significantly higher in patients achieving near-pCR than that in patients achieving pCR (HR = 3.01,95%CI:1.34–7.01, P = 0.008, Fig. 1a). A total of 15 (5.1%) patients had death. The 3-year OS rates of the pCR group and the near-pCR group were 96.6% and 96.3%, respectively. The 5-year OS

rates of the pCR and near-pCR groups were 94.3% and 89.6%, respectively. There was no statistical difference of OS between the two cohorts (HR = 1.69,95%CI:0.61–4.67, $P = 0.304$, Fig. 1b).

1.4 Predictive factors of RFS in patients achieving pCR

Table 3 shows the results of the analyses for factors associated with RFS of patients achieving pCR. Clinical lymph node status (cN) before NAC was a significant covariate in the univariate for RFS in patients achieving pCR ($P < 0.001$). The 5-year RFS rates for cN0-N2 and cN3 patients who achieved pCR were 98.0% and 82.7%, respectively. cN3 was an independent factor of higher risk for recurrence on the multivariate analysis (Fig. 2, HR = 9.8, 95%CI:2.1–44.5, $P = 0.003$). Age at diagnosis, tumor size at diagnosis, subtype of breast cancer and other factors showed no significant association with RFS of patients who achieved pCR ($P \geq 0.05$).

Table 3
Analysis of predictive factors for RFS in patients who achieved pCR

	Univariate analysis				Multivariate analysis	
	N	Events	5-Year RFS rate (%) (95% CI)	*P* value	HR (95% CI)	*P* value
Total	173	9				
Age				0.416		
40	44	3	92.0 (83.7–100)			
≥ 40	129	6	95.5 (88.2–99.1)			
Menopausal status				0.919		
Premenopausal	101	5	95.8 (91.9–99.9)			
Postmenopausal	72	4	93.3 (87.0-100)			
cT				0.730		
T1-2	123	5	96.3 (92.8–99.9)			
T3-4	50	4	91.1 (83.0-100)			
cN				0.000		
N0-2	136	3	98.0 (95.1–100)		reference	
N3	37	6	82.7 (70.9–96.3)		9.8(2.1–44.5)	**0.003**
ER status				0.154		
Negative	128	5	96.2 (92.5–100)		reference	
Positive	45	4	89.7 (80.5–99.9)		0.9 (0.2–4.2)	0.939
PR status				0.151		
Negative	115	4	96.6 (92.8–100)		reference	
Positive	58	5	90.7 (83.2–98.8)		2.2 (0.5–9.1)	0.296
HER2 status				0.737		

Abbreviation:RFS:recurrence-free survival;pCR:pathological complete response;cT:clinical tumour size; cN: clinical lymph node status;ER: estrogen receptor; PR: progesterone receptor; HER2:human epidermal growth factor receptor type 2; Ki67:Ki67 index; NAC:neoadjuvant chemotherapy.

*HER2 positive included luminal B HER2 + and non-luminal HER2+.

	Univariate analysis				Multivariate analysis	
Negative	86	4	95.0 (90.3–99.9)			
Positive	87	5	94.2 (88.6–100)			
Ki67				0.623		
＜50	72	5	93.0 (86.5–100)			
≥ 50	92	4	95.5 (91.2–99.9)			
unknown	9	0	---			
Breast cancer subtype				0.750		
Luminal	29	2	92.1 (82.3–100)			
HER2 positive*	87	5	94.2 (88.6–100)			
Triple negative	57	2	96.4 (91.6–100)			
Chemotherapy regimens of NAC				0.063		
Anthracycline and taxane	40	5	87.4 (77.7–98.4)		reference	
Taxane and platinum	117	3	98.2 (95.9–100)		0.3 (0.1–1.4)	0.116
others	16	1	85.7 (63.3–100)		2.1 (0.2–22.7)	0.534
Cycle number of NAC				0.591		
＜4	2	0	---			
4–6	153	9	94.0 (90.0-98.2)			
＞6	18	0	---			
Surgery of breast cancer				0.359		
Breast-conserving surgery	41	3	94.5 (87.4–100)			
Mastectomy	132	6	94.8 (90.7–99.0)			
Surgery of lymph nodes				0.873		

Abbreviation:RFS:recurrence-free survival;pCR:pathological complete response;cT:clinical tumour size; cN: clinical lymph node status;ER: estrogen receptor; PR: progesterone receptor; HER2:human epidermal growth factor receptor type 2; Ki67:Ki67 index; NAC:neoadjuvant chemotherapy.

*HER2 positive included luminal B HER2 + and non-luminal HER2+.

	Univariate analysis			Multivariate analysis
Sentinel lymph node biopsies	28	1	100	
Axillary lymph node dissection	145	8	93.8 (89.6–98.1)	
Adjuvant radiation				0.695
Yes	125	7	94.2 (89.8–98.9)	
No	48	2	95.5 (89.5–100)	
Adjuvant endocrine				0.234
Yes	67	5	91.5 (84.6–99.0)	
No	106	4	96.5 (92.5–100)	
Abbreviation:RFS:recurrence-free survival;pCR:pathological complete response;cT:clinical tumour size; cN: clinical lymph node status;ER: estrogen receptor; PR: progesterone receptor; HER2:human epidermal growth factor receptor type 2; Ki67:Ki67 index; NAC:neoadjuvant chemotherapy.				
*HER2 positive included luminal B HER2 + and non-luminal HER2+.				

1.5 Predictive factors of RFS in patients achieving near-pCR

Table 4 shows the results of the analyses for the factors associated with RFS of patients achieving near-pCR. cN before NAC was a significant covariate in the univariate for RFS in patients achieving near-pCR (Fig. 3, P = 0.036). The 5-year RFS rates for cN0-2 and cN3 patients who achieved near-pCR were 88.5% and 71.1%, respectively. Miller-Payne grade and the size of residual disease after NAC showed no significant association with RFS of patients who achieved near-pCR ($P \geq 0.05$). There were no other factors significant at the 20% level in the univariate analyses of RFS for patients achieving near-pCR, so we did not conduct multivariate analyses further.

Table 4
Analyses of predictive factors for RFS in patients who achieved near-pCR

	Univariate analyses			
	N	Events	5-Year RFS rate (%) (95% CI)	*P* value
Total	119	17		
Age				0.251
40	51	9	81.5 (70.6–94.1)	
≥ 40	68	8	88.5 80.8–97.0)	
Menopausal status				0.467
Premenopausal	81	13	84.7 (76.7–93.5)	
Postmenopausal	38	4	87.6 (76.7–100)	
cT				0.506
T1-2	70	12	83.6 (74.6–93.6)	
T3-4	49	5	88.5 (79.4–98.6)	
cN				**0.036**
N0-2	101	12	88.5 (82.0-95.5)	
N3	18	5	71.1 (52.6–96.1)	
ER status				0.720
Negative	75	10	86.5 (78.6–95.2)	
Positive	44	7	83.8 (72.7–96.7)	
PR status				0.411
Negative	59	10	83.4 (74.1–94.0)	
Positive	60	7	87.2 (78.2–97.4)	
HER2 status				0.300
Negative	56	6	90.8 (82.5–99.9)	

Abbreviation:RFS:recurrence-free survival;near-pCR:near-pathological complete response;cT:clinical tumour size; cN: clinical lymph node status;ER: estrogen receptor; PR: progesterone receptor; HER2:human epidermal growth factor receptor type 2; Ki67:Ki67 index; NAC:neoadjuvant chemotherapy.

*HER2 positive included luminal B HER2 + and non-luminal HER2+.

**2 patients with Miller-Payne grade 5 were ypT0N1miM0.

Univariate analyses				
Positive	63	11	80.9 (71.3–91.8)	
Ki67				0.740
50	61	10	83.1 (73.5–93.9)	
≥ 50	50	6	85.9 (76.0-97.2)	
unknow	8	1	—	
Breast cancer subtype				0.583
Luminal	30	5	80.3 (66.2–97.5)	
HER2 positive*	56	6	90.8 (82.5–99.9)	
Triple negative	33	6	81.4 (68.9–96.0)	
Treatment of NAC				0.476
Anthracycline and taxane	46	5	90.5 (82.0-99.8)	
Taxane and platinum	58	10	83.0 (73.4–93.9)	
others	15	2	77.1 (53.5–100)	
Cycle number of NAC				0.944
4	8	1	75.0 (42.6–100)	
4–6	95	14	86.0 (79.0-93.8)	
6	13	2	81.5 (61.1–100)	
Surgery of breast cancer				0.610
Breast-conserving surgery	26	3	87.8 (75.8–100)	
Mastectomy	93	14	84.6 (76.8–93.1)	
Surgery of lymph nodes				0.432
Sentinel lymph node biopsies	21	4	76.3 (58.0-100)	
Axillary lymph node dissection	98	13	87.3 (80.5–94.7)	

Abbreviation:RFS:recurrence-free survival;near-pCR:near-pathological complete response;cT:clinical tumour size; cN: clinical lymph node status;ER: estrogen receptor; PR: progesterone receptor; HER2:human epidermal growth factor receptor type 2; Ki67:Ki67 index; NAC:neoadjuvant chemotherapy.

*HER2 positive included luminal B HER2 + and non-luminal HER2+.

**2 patients with Miller-Payne grade 5 were ypT0N1miM0.

Univariate analyses				
ypTNM after NAC				0.942
ypT1miN0M0	5	1	80.0(51.6–100)	
ypT1aN0M0	73	11	86.1(78.0–95.0)	
ypT1bN0M0	39	5	85.0(73.5–98.2)	
ypT0N1miM0	2	0	—	
Miller-Payne grade				0.334
1 ~ 3	42	4	89.2(79.8–99.8)	
4 ~ 5**	77	13	83.8 (75.5–93.1)	
Adjuvant radiation				0.545
Yes	86	12	86.1 (78.7–94.1)	
No	33	5	83.8 (70.4–99.8)	
Adjuvant endocrine				0.925
Yes	61	9	84.1 (74.5–95.9)	
No	58	8	86.9 (78.2–96.5)	
Abbreviation:RFS:recurrence-free survival;near-pCR:near-pathological complete response;cT:clinical tumour size; cN: clinical lymph node status;ER: estrogen receptor; PR: progesterone receptor; HER2:human epidermal growth factor receptor type 2; Ki67:Ki67 index; NAC:neoadjuvant chemotherapy.				
*HER2 positive included luminal B HER2 + and non-luminal HER2+.				
**2 patients with Miller-Payne grade 5 were ypT0N1miM0.				

Discussion

In this retrospective study of 292 patients achieving pCR and near-pCR after NAC, the recurrence pattern of patients was described, and the vast majority of recurrence occurred within 36 months from onset of NAC. This study found that the risk for recurrence of patients achieving near-pCR after NAC was higher than those achieving pCR. Besides, cN3 before NAC was identified as a robust predictive factor of RFS for patients achieving pCR and near-pCR.

The 5-year RFS rate of pCR was 94.6% in our study, which was consistent with previous studies [13–15]. The sub-study of EORTC 10994/BIG 1 – 00 phase III trial including 283 patients found that clinical tumour size was the only predictor for distant recurrence-free interval (DRFI) after pCR[15]. In the research from the MD Anderson group, the authors identified that clinical stage IIIB-C and inflammatory breast cancer,

premenopausal status and resection of fewer than 10 lymph nodes were associated with an increased risk of developing distant metastasis for patients achieving pCR[16]. Since cN contributes to the clinical stage, as a result, our study was partly consistent with the MD Anderson' research. Asaoka M and colleges' research also found that lymph node metastasis before NAC was the only predictor of cancer recurrence on multivariate analyses for patients achieving pCR[17].

The 5-year RFS rate of near-pCR was 85.6%, which was 9% lower than that of patients achieving pCR, but the OS of the two cohorts had no significant difference. In Spring L' Meta analysis [18], which included 27,895 patients from 52 publications, showed that patients with residual disease after NAC had a 5-year DFS rate of 67%, which was much lower compared with the near-pCR population (85.6%) in our study. This illustrated the fact that it was necessary to distinguish the near-pCR population from the residual disease. There has been controversy regarding the definition of near-pCR in the past few years[19]. In Cheng Q's study, near-pCR was defined as residual tumor volume < $1cm^3$[20]. However, Lee H and colleagues defined near-pCR as tumor size ≤ 0.5 cm[21]. In our study, near-pCR was defined as the residual tumor being ≤ 1cm in size in the breast (ypT1mi/1a/1bN0), or no residual invasive carcinoma in the breast yet existing micrometastasis in lymph node (ypT0/isN1mi).

To our best knowledge, this study is the first one to report the potential predictive factors of RFS for patients achieving near-pCR. We found that cN3 was an independent factor of higher risk for recurrence in the near-pCR subgroup, which was consistent with the pCR subgroup. The 5-year RFS rates for cN0-2 and cN3 patients who achieved near-pCR were 88.5% and 71.1%, respectively (P = 0.036). According to AJCC 8th edition staging system of breast cancer, cN3 is defined as metastasis to ipsilateral infraclavicular/supraclavicular lymph node(s), or metastasis to ipsilateral internal mammary lymph node(s) and axillary lymph node(s). There is controversy regarding the treatment of the local supraclavicular and internal mammary lymph node(s). It is difficult to remove the supraclavicular lymph node(s) and internal mammary lymph node(s) during the surgery. Radiation therapy is usually applied to deal with the supraclavicular and internal mammary lymph node(s) involvement. However, it is difficult to evaluate whether the status of no evidence of disease (NED) is reached. In recent years, growing interest was focused on post-NAC treatment, and some trials noted that reinforce adjuvant treatment could improve prognosis for patients with residual disease. In the subset of CREATE-X, TNBC patients with residual invasive disease who received capecitabine had a 5-year DFS rate of 69.8%, 13.7% higher than the control group (HR = 0.58, 95% CI:0.39–0.87)[8]. In the KATHERINE clinical trial, the invasive DFS at 3 years of HER2-positive breast cancer patients with residual invasive disease who received T-DM1 was 88.3%, compared with 77.0% of the trastuzumab group (HR = 0.5, P < 0.001)[9]. However, numerous post-NAC clinical trials incorporated patients whose residual disease of at least 1.0 cm or node positive disease, excluding patients that achieved near-pCR. Our study showed that patients with near-pCR still had a certain risk of recurrence. Adjuvant therapy to minimize the risk of recurrence for patients with near-pCR is needed to be illuminated in further prospective researches.

Our study also has several limitations. First, it was a retrospective study, therefore selection bias was inevitable. Second, because the number of death events was small, we did not conduct analysis on the

predictive factors of OS in patients achieving pCR and near-pCR respectively.

Conclusions

Patients achieving pCR had excellent outcomes. The recurrence risk of patients achieving near-pCR after NAC was higher than that of patients achieving pCR. The vast majority of recurrence occurred within 3 years from onset of NAC. Patients with cN3 before NAC had a higher risk of developing locally and distant metastasis even achieving pCR or near-pCR after NAC. It is worthwhile to monitor closely for patients with cN3, especially in the first 3 years.

Abbreviations

pCR
Pathological complete response
Near-pCR
Near-pathological complete response
NAC
Neoadjuvant chemotherapy
CHCAMS
The Cancer Hospital, Chinese Academy of Medical Sciences
HER2
Human epidermal growth factor receptor type 2
TNBC
Triple-negative breast cancer
RFS
recurrence-free survival
cT
Clinical tumour size
cN
Clinical lymph node status
DFS
Disease-free survival
OS
Overall survival
ER
Estrogen receptor
PR
Progesterone receptor
Ki67
Ki67 index

IHC
Immunohistochemistry
FISH
Fluorescence in situ hybridization
TKI
Tyrosine Kinase Inhibitor.

Declarations

Ethics approval and consent to participate

This study was performed in accordance with Declaration of Helsinki and was approved by the Institutional Review Board of the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College. As this study was retrospective and collected the existing data, the informed consent was waived by the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College.

Consent for publication

Not applicable.

Availability of data and materials

For original data, please contact zppumc@163.com.

Competing interests

All authors have declared that no competing interest exists.

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Authors' contributions

PZ contributed to the study concept, design, patient management and revised the manuscript. XYQ contributed to data collection, data analysis and drafted the manuscript. MX revised the manuscript. PY, JYW, YL, YF, RGC, QL, SSC, QL, FM and BH X participated in patient management. All authors approved the final version of the manuscript.

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Figures

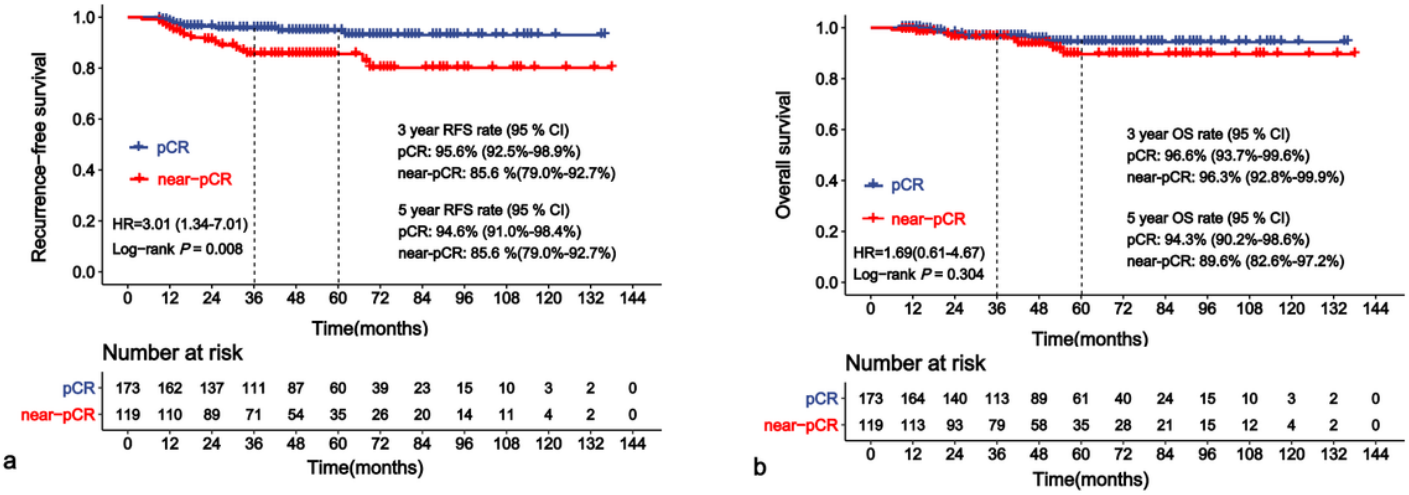

Figure 1

a. Kaplan–Meier curve showing recurrence-free survival (RFS) according to the status after neoadjuvant chemotherapy(NAC):pathological complete response(pCR) vs. near-pathological complete response(near-pCR) b. Kaplan–Meier curve showing overall survival (OS) according to the status after neoadjuvant chemotherapy(NAC) :pathological complete response(pCR) vs. near-pathological complete response(near-pCR)

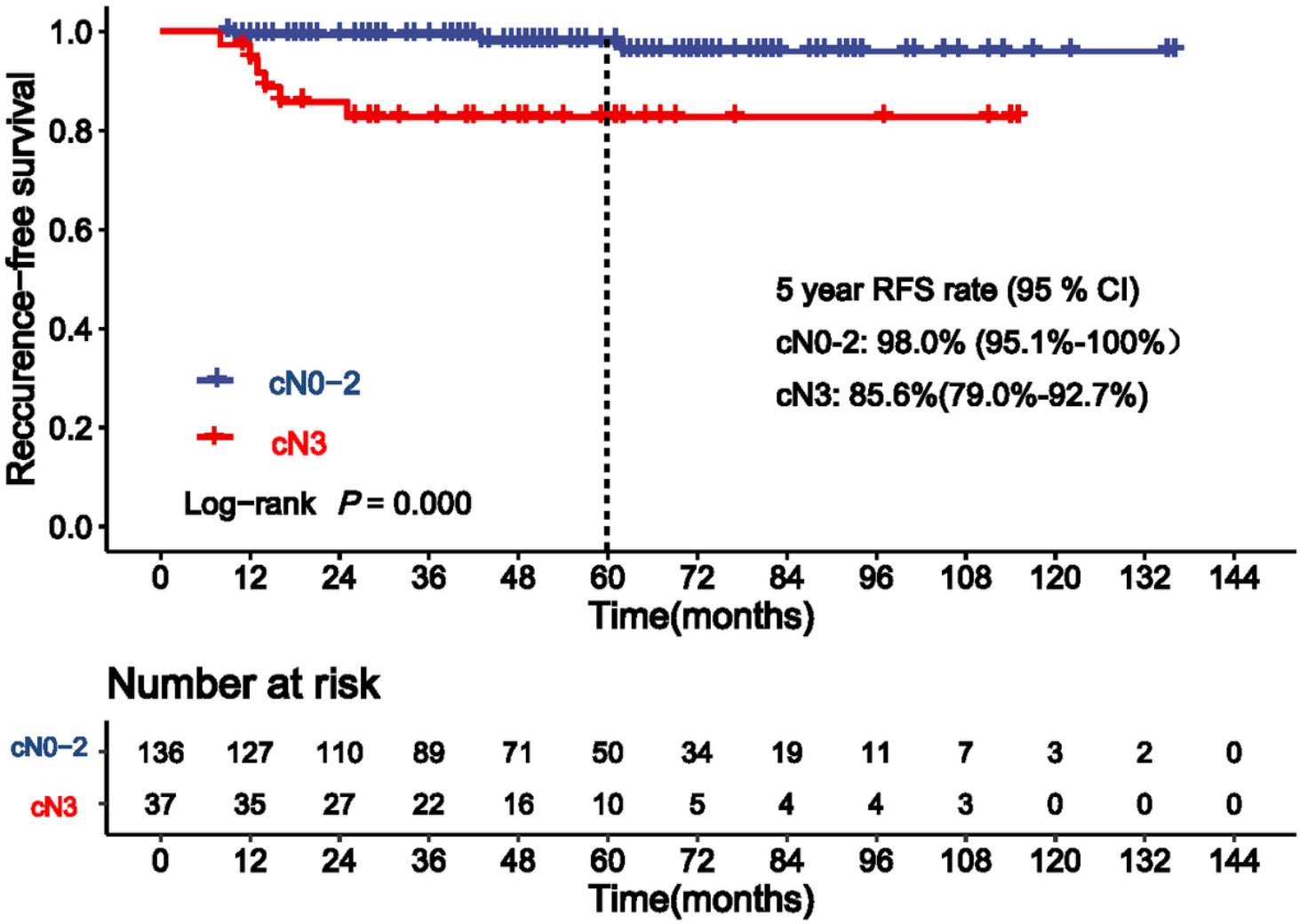

Figure 2

Kaplan–Meier curve showing recurrence-free survival (RFS) of patients achieving pathological complete response(pCR) according to clinical lymph node status (cN)

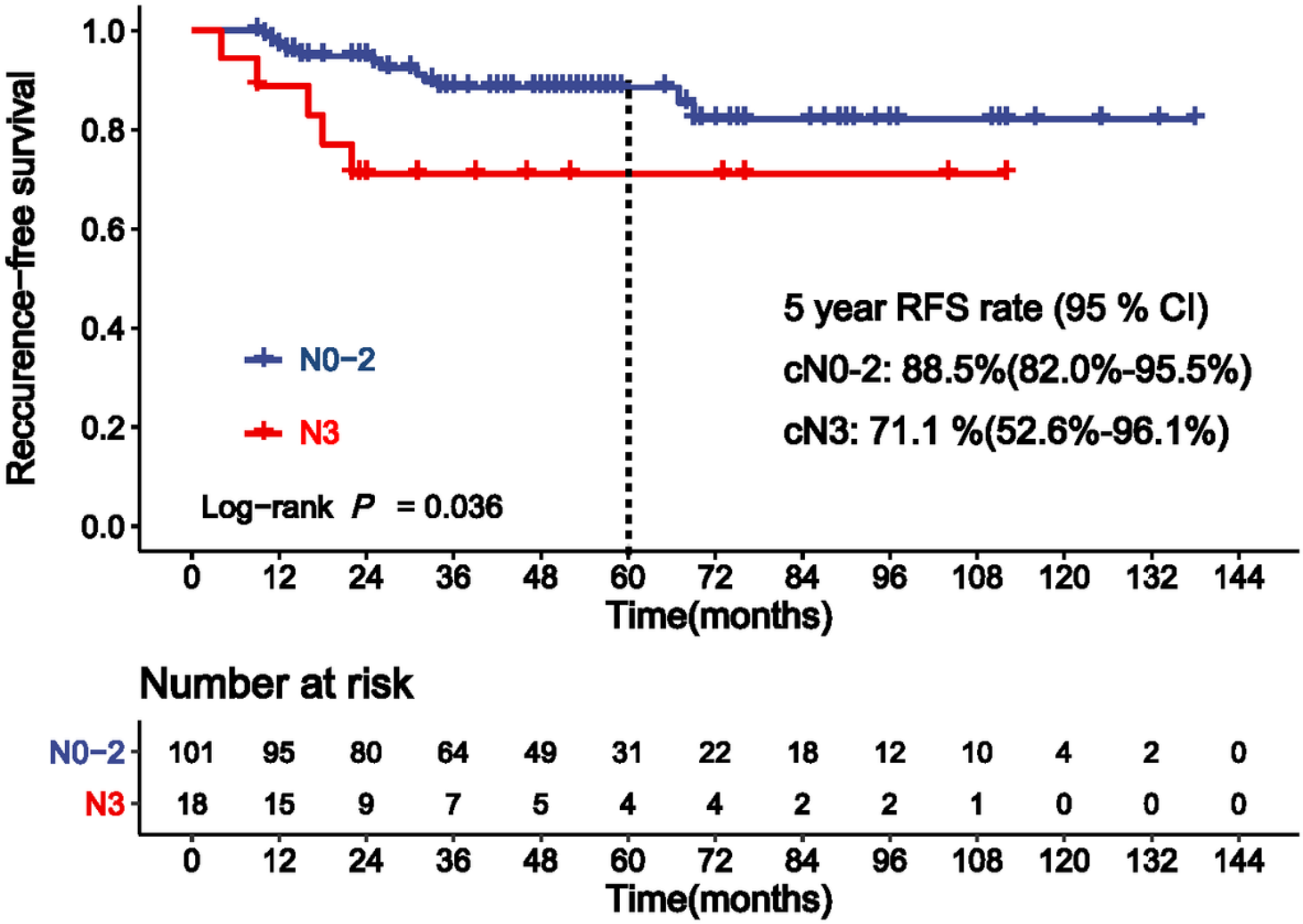

Figure 3

Kaplan–Meier curve showing recurrence-free survival (RFS) of patients achieving near-pCR according to clinical lymph node status (cN)