Original Article

Prognostic factors of axillary lymph node-positive patients in clinical stage II and III breast cancer after neoadjuvant chemotherapy

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Background: Surgery following neoadjuvant chemotherapy (NAC) is increasingly utilized for breast cancer treatment with respect to downstage and recurrent risk reduction. However, there are some uncertainties about the solutions of adjuvant radiotherapy (design of RT field and indication in low-risk patients) in patients after NAC, especially in clinically node-positive patients. The objective of this study is to identify the risk factors of loco-regional recurrence (LRR), relapse and overall survival (OS) regarding tumor response post-NAC in this institution.

Methods: From 2007 to 2015, 90 patients with newly diagnosed clinical stage II (n=44) or III (n=46) breast cancer and pathological positive lymph nodes who received chemotherapy followed by breast conserving surgery or mastectomy, adjuvant radiotherapy, and some with adjuvant systemic therapy were identified. All of them received anthracycline-based or taxane-based chemotherapy, external beam radiotherapy and systemic treatment including target or hormone therapy if indicated.

The patient characteristics included clinical T/N stage, pathologic T/N stage, response after NAC, tumor grade, surgical margin, the presence or absence of lymphovascular invasion and extracapsular extension, the total number of lymph nodes dissection, the positive lymph nodes ratio (pLNR), tumor biomarker status [estrogen receptor (ER)/progesterone receptor (PR)/human epidermal growth factor receptor 2 (HER-2)], and adjuvant chemotherapy/target therapy or not. Univariate and multivariate analyses for risks of loco-regional recurrence (LRR), relapse (any local, regional or distant recurrence), and overall survival (OS) and the survival curves of LRR and relapse were performed.

Results: After a median follow-up duration of 62 months (7–125 months), the multivariate analysis for risks of LRR showed that the status of clinical lymph nodes (cN2: HR =6.07, P=0.046; cN3: HR =30.22, P=0.001), response subgroups (stable disease: HR =3.01, P=0.047; progressive disease: HR =10.76, P<0.001), and pLNR (67–100%: HR =4.32, P=0.025) have statistical significance. The multivariate analysis for risks of relapse also showed that the status of clinical lymph nodes (cN1 micro/N1: HR =3.97, P=0.037; cN2: HR =4.06, P=0.053; cN3: HR =10.39, P=0.005), response subgroups (progressive disease: HR =3.73, P=0.008) and pLNR (67–100%: HR =3.02, P=0.032) have statistical significance. The multivariate analysis of OS only showed the tumor biomarker status of triple-negative breast cancer (TNBC) (HR =3.04, P=0.048) has statistical significance.

Conclusions: In this study, we recorded poor therapeutic response, advanced clinically positive lymph nodes, and higher proportional positivity of dissected lymph nodes showing poor outcome regarding the loco-regional control and relapse-free survival among patients with positive axillary lymph nodes after NAC.

Keywords: Breast cancer; loco-regional recurrence (LRR); lymph node ratio; neoadjuvant chemotherapy (NAC); risk factors

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Introduction

Surgery following neoadjuvant chemotherapy (NAC) is increasingly utilized for breast cancer treatment for various reasons. First, NAC results in loco-regional downstage and promotes breast conserving surgery (BCS) for better cosmetic outcomes (1-3). Second, the chemotherapeutic response can be tested before tumor excision via this approach, which helps avoid any ineffective adjuvant or NAC regimens and their resultant toxicities. In other words, earlier systemic treatment with effective regimens helps reduce risk of recurrence. Third, NAC allows selection of the optimal treatment option for individualized patient subgroups based on their therapeutic response and prognostic risks. However, as compared to the effectiveness of performing adjuvant radiotherapy after surgery, this approach involves uncertainties regarding the solutions of adjuvant radiotherapy (design of RT field and indication in low risk patients) in patients receiving NAC [e.g., the indication of treatment coverage of the axilla region regarding the dissected lymph nodes and post-mastectomy radiotherapy (PMRT) for low-risk patients with complete response]. In the past, most recurrent risks indicated by high-level evidence were those patients receiving adjuvant chemotherapy and radiotherapy following primary surgery. However, till date, when originally applied in patients with locally advanced disease, NAC has subsequently presented its extended indications even in the early stage disease.

Good response after NAC [e.g., pathological complete response (pCR)] is a strong predictor of its favorable outcome (1,4-6). The predictors reported in previous studies on primary surgery may not be accurate for assessing recurrent risks which are required to make decisions regarding loco-regional radiotherapy.

The impact of axillary lymph node status and correlated risk factors on the loco-regional events is also not well documented. Even the National Comprehensive Cancer Network (NCCN) guidelines of 2018.V1 state that "treat any part of axillary bed at risk" without interpretation of the types of risks in detail. The objective of this study was to identify the risk factors of loco-regional recurrence (LRR), relapse (any local, regional, or distant recurrence) and the overall survival (OS) with respect to tumor response after NAC in patients treated at our institution.

Methods

Patient characteristics

We retrospectively reviewed the patients treated at our institute between 2007 and 2015; 190 non-metastatic patients had received neoadjuvant systemic treatment, surgery, and adjuvant radiotherapy. The exclusion criteria were previous breast cancer disease (N=1), synchronous bilateral breast cancer disease (N=1), non-pure infiltrating ductal carcinoma (N=6), neoadjuvant treatment by hormone therapy alone (N=2), no adjuvant radiotherapy in this institute (N=2), no follow-up (N=3), human epidermal growth factor receptor 2 (HER-2) positive patients without trastuzumab (Herceptin®) prescription (N=6) and no residual lymph node disease (N=79). Patients were considered positive for HER-2 when there was a strong over-expression of HER2 immunohistochemical study (3+) or gene amplification by fluorescence *in situ* hybridization (FISH) in samples obtained by biopsy or definitive surgery.

In total, 90 patients were found eligible for the final analysis in this study. The patient characteristics included diagnosed at age ≤/>50 years, surgery method as BCS or total mastectomy, clinical T/N categories and stage, pathological T/N categories, therapeutic response after NAC, the number and positive lymph nodes ratio, tumor grading, surgical margin (≤/> 1 mm), the presence or absence of extracapsular extension (ECE), the presence or absence of lymphovascular invasion (LVI), tumor biomarker status [such as estrogen receptor (ER)/ progesterone receptor (PR)/HER-2], and adjuvant chemotherapy/target therapy.

Diagnostic method and operation details

The initial assessment of axillary disease was performed by ultrasound or aspiration cytology of the lymph nodes. BCS

or total mastectomy with axillary lymph node dissection (ALND) and/or sentinel lymph node biopsy (SLNB) was performed by surgeons according to the institute's guidelines for treating breast cancer.

Systemic therapy

According to the clinical practice guidelines of this institute, neoadjuvant anthracycline-based chemotherapy with or without taxane was administered for 2–6 cycles (most commonly 4 cycles). The decision whether adjuvant chemotherapy should be administrated depended on previous incomplete neoadjuvant cycles and response after NAC, and the total neoadjuvant and adjuvant chemotherapy course comprised 8 cycles. Trastuzumab (Herceptin®) every 3 weeks for a total duration of a year in neoadjuvant and adjuvant periods was prescribed for patients with strong over-expression or gene amplification of HER2 status. All patients received surgery after an NAC course of 2–6 weeks. Hormone therapies of tamoxifen, aromatase inhibitor, or GnRH inhibitor were prescribed for patients with positive ER or PR status for at least 5 years after adjuvant radiotherapy.

Response assessment

We compared the initial tumor size by ultrasound (preferred) or MRI (in case of no ultrasound), which were assessed by a certified surgical oncologist or radiologist, and the post-treatment tumor size was assessed by final pathological report. The response subgroups were defined as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) with reference to the response evaluation criteria in solid tumor (RECIST 1.1) as a reference (7). CR was defined as no residual invasive disease, such as ypT0/Tis and ypN0 (6).

Radiotherapy technique

Adjuvant radiotherapy for the whole breast or chest wall with lymphatic areas [supra/infraclavicular fossae (SCF/ICF) and internal mammary chain (IMC)] was performed using 2D-radiotherapy (2DRT), 3D-conformal RT (3DCRT), intensity-modulated radiotherapy (IMRT), or volumetric arc therapy (VMAT). For patients undergoing BCS, a total radiation dose of 45–50.4 Gy (1.8–2.0 Gy daily fraction) was delivered to the whole breast, with or without regional lymphatic areas (SCF/ICF and IMC), followed by a 10–16 Gy boost to the tumor bed. For patients undergoing total mastectomy, a total radiation dose of 50–50.4 Gy (1.8–2.0 Gy per fraction) was delivered to the chest wall, with or without regional lymphatic areas (SCF/ICF and IMC). The patients who had close margin (≤1 mm) and/or skin invasion in the mastectomy group were allowed to receive tumor bed boost with 10–16 Gy. All patients with the axillary disease after NAC received RT to the regional lymphatic areas (SCF, ICF, and IMC).

Statistical analysis

The Kaplan-Meier survival analysis was performed and compared by log-rank test. Univariate and multivariate analyses for LRR, relapse-free survival (RFS), and OS using Cox-proportional hazard model were performed to estimate the hazard ratio (HR) and 95% confidence interval (CI). RFS is defined as any disease recurrence (local, regional, or distant); however, death was censored (data not shown). P value ≤0.05 was considered to indicate statistical significance. Statistical analyses were calculated using the IBM SPSS Statistics for MAC (Version 22.0 IBM Corp., Armonk, NY).

Institutional Review Board (IRB)

The study was approved by the Breast Cancer Multidiscipline Group of Changhua Christian Hospital (CCH), and the ethical approval for the same was obtained from the committee on human experimentation of the same institution (CCH IRB No. 180313).

Results

Patients

A total of 90 patients with clinical stages II and III invasive ductal carcinoma received neoadjuvant anthracycline-based chemotherapy with or without taxane and target therapy, followed by curative surgery and adjuvant radiotherapy. With a median follow-up duration of 62 months (7–125 months), the median age at diagnosis was 49 years (25–76 years) in the entire cohort. Of these patients, 44 (49%) women had clinical stage II disease and 46 (51%) had clinical stage III disease. The subgroups on the basis of clinical lymph node status included: N0, N1 micro/N1, N2, and N3, which were observed in 11 (12%), 57 (63%), 16 (18%), and 6 (7%) patients. The number and percentage

of women with BCS, diagnosed at >50 years, primary tumor at the left side, and the primary tumor location at UOQ were 24 (27%), 37 (41%), 42 (47%) and 39 (43%), respectively. The numbers and percentages of the factors such as <10 dissected lymph nodes, surgical margin of >1 mm, presence of lymphovascular invasion and presence of extracapsular extension of lymph nodes were 19 (21%), 67 (74%), 71 (79%) and 50 (56%), respectively, as per the final pathological report. The numbers of patients with positive lymph nodes ratio of 0–33%, 34–66% and 67–100% were 52 (58%), 20 (22%) and 18 (20%), respectively.

After NAC, the comparison of initial and post-treatment size demonstrated PR, SD, and PD in 52 (58%), 28 (31%) and 10 (11%) patients, respectively. The tumor types categorized by ER/PR/HER2 status, referred to as luminal A/B, Her2 positive and triple-negative breast cancer (TNBC), were observed in 50 (56%), 29 (32%), and 11 (12%) patients, respectively. There were 39 (43%) patients receiving the adjuvant chemotherapy and/or target therapy. Patient characteristics are summarized in *Table 1*.

Outcome and prognostic significance

Univariate analysis of risks of LRR showed that clinical N category (cN3: HR =8.43, P=0.015), therapeutic response after NAC (SD: HR =2.54, P=0.038; PD: HR =5.32, P=0.002), dissected lymph nodes (≥10 nodes: HR =0.37, P=0.018) and positive lymph nodes ratio (67–100%: HR =5.14, P<0.001) are statistically significant. Multivariate analysis of risks of LRR also showed that the status of clinical lymph nodes (cN2: HR =6.07, P=0.046; cN3: HR =30.22, P=0.001), response subgroups (SD: HR =3.01, P=0.047; PD: HR =10.76, P<0.001), and positive lymph nodes ratio (67–100%: HR =4.32, P=0.025) are statistically significant (*Table 2*).

Univariate analysis of risks of relapse also showed that the clinical N category (cN3: HR =6.73, P=0.015), therapeutic response after NAC (PD: HR =3.09, P=0.012), pathological N category (pN3a: HR =2.72, P=0.025), and positive lymph nodes ratio (67%–100%: HR =3.65, P<0.001) are statistically significant. The clinical N categories (cN1 micro/N1: HR =3.97, P=0.037, cN3: HR =10.39, P=0.005), therapeutic response after NAC (PD: HR =3.73, P=0.008) and positive lymph nodes ratio (67–100%: HR =3.02, P=0.032) also yielded statistical significance in the multivariate analysis of risks of relapse. Moreover, the clinical N category cN2 showed a statistical trend (HR =4.06, P=0.053) (*Table 3*).

All patients in this cohort who died had distant metastases. The risk factors affecting OS with statistical significance in the univariate analysis were the clinical N3 category (HR =10.73, P=0.042) and tumor type of TNBC (HR =4.09, P=0.006). However, only the tumor type TNBC (HR =3.04, P=0.048) showed statistical significance in the multivariate analysis (*Table 4*).

The survival curves for LRR-free survival and RFS stratified by the therapeutic response after NAC, the positive lymph nodes ratio and the clinical N status compared by log-rank test showed statistical significance (P<0.05). The survival curves for RFS stratified by clinical N status showed a statistical trend (P=0.057) (*Figure 1*).

Discussion

Significant predictors of LRR for patients treated primarily with surgery are well documented in the literature. Among these predictors, the pathologic status of axillary lymph nodes, number of positive lymph nodes, and even adequacy of axillary dissection are shown to strongly predict LRR. However, the issues with these prognostic factors and the impact of regional nodal irradiation have rarely been addressed in patients primarily treated with NAC.

In this study, we aimed to examine the risk factors of LRR and relapse for patients receiving curative surgery following NAC to decide whether the level I axillary lymphatic region should be included in the target radiation field. Previous studies in non-NAC scenarios showed that dissection of at least 10 lymph nodes is adequate ALND (8-16), which is advantageous for disease control and OS (8-13,16).

There was no indication of radiotherapy for the level I axillary region in patients with adequate ALND because of significant treatment sequelae of a combination of ALND and axillary RT (17,18). Considering the serious side-effects of ALND, axillary RT gradually replaced ALND in clinical node-negative but pathologically SLNB positive patients (19).

Numbers of dissected lymph nodes

It is well known that the number of positive lymph nodes is a risk factor for disease control in pathologically node-positive patients after NAC (20,21). However, pathologically negative node after NAC may not indicate lack of residual tumor in the lymph node. Inadequate dissection or change in lymphoid tissue after NAC may also affect the pathological examination under the microscope.

In fact, there may be other reasons leading to inadequate

Table 1 Patient characteristics

Characteristics	N	%
Age (years)		
≤50	53	59
>50	37	41
Surgery		
BCS	24	27
Mastectomy	66	73
Tumor laterality		
Left	42	47
Right	48	53
Tumor location		
UOQ	39	43
Non-UOQ	51	57
Clinical stage		
c stage II	44	49
c stage III	46	51
Clinical T		
cT1–2	51	57
cT3	24	27
cT4	15	17
Clinical N		
cN0	11	12
cN1 micro/N1	57	63
cN2	16	18
cN3	6	7
Response		
Partial	52	58
Stable	28	31
Progression	10	11
Pathological T		
T1–2	10	11
T3	53	59
T4	27	30
Pathological N		
N0ihc/mi/1A	51	57
N2a	29	32
N3a	10	11
Dissected lymph nodes		
1–3#	3	3
4–9#	16	18
≥10#	71	79
LN positive ratio		
0–33%	52	58
34–66%	20	22
67–100%	18	20
Grade		
≤1	19	21
2	49	54
3	22	24
Surgical margin (mm)		
>1	67	74
≤1	23	26
Lymphovascular invasion		
No	19	21
Yes	71	79
Extracapsular extension		
No	40	44
Yes	50	56
Tumor type		
ER/PR+ Her2–	50	56
ER/PR+ Her2+	20	22
ER/PR– Her2+	9	10
TNBC	11	12
Adjuvant chemotherapy or target therapy		
No	51	57
Yes	39	43

BCS, breast conserving surgery; LN, lymph nodes; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor type2; TNBC, triple negative breast cancer.

Table 2 Cox proportional-hazards regression analysis of loco-regional recurrence

Characteristics	Total	LRR		Univariate analysis				Multivariate analysis (adjusted)			
		N	%	HR	95% CI		P value	HR	95% CI		P value
					Lower	Upper			Lower	Upper	
Age (years)											
≤50	53	13	24.5	1							
>50	37	13	35.1	1.26	0.86	1.86	0.236				
Surgery											
BCS	24	6	25.0	1							
Mastectomy	66	20	30.3	1.37	0.55	3.41	0.500				
Clinical stage											
c stage II	44	13	29.5	1							
c stage III	46	13	28.3	0.92	0.43	1.98	0.830				
Clinical T											
cT1–2	51	13	25.5	1							
cT3	24	8	33.3	1.17	0.49	2.83	0.725				
cT4	15	5	33.3	1.34	0.48	3.77	0.574				
Clinical N											
cN0	11	2	18.2	1				1			
cN1 micro/N1	57	13	22.8	1.44	0.33	6.40	0.630	3.27	0.61	17.63	0.168
cN2	16	7	43.8	3.14	0.65	15.20	0.154	6.07	1.04	35.61	0.046*
cN3	6	4	66.7	8.43	1.51	47.21	0.015*	30.22	4.27	213.62	0.001*
Response											
Partial	52	9	18.3	1				1			
Stable	28	11	39.3	2.54	1.05	6.13	0.038*	3.01	1.02	8.92	0.047*
Progression	10	6	60.0	5.32	1.88	15.00	0.002*	10.76	3.14	36.86	<0.001**
Pathological T											
T1–2	10	2	20.0	1.00							
T3	53	13	24.5	1.24	0.28	5.50	0.778				
T4	27	11	40.7	2.35	0.52	10.61	0.267				
Pathological N											
N0ihc/mi/1A	51	12	23.5	1				1			
N2a	29	9	31.0	1.44	0.61	3.42	0.409	0.48	0.16	1.46	0.197
N3a	10	5	50.0	2.63	0.92	7.49	0.071	0.58	0.15	2.23	0.423
Dissected lymph node											
<10#	19	9	47.4	1							
≥10#	71	17	23.9	0.37	0.17	0.84	0.018*				

Table 2 (*continued*)

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Characteristics	Total	LRR		Univariate analysis				Multivariate analysis (adjusted)			
		N	%	HR	95% CI		P value	HR	95% CI		P value
					Lower	Upper			Lower	Upper	
LN+ ratio											
0–33%	52	9	17.3	1				1.00			
34–66%	20	6	30.0	2.09	0.74	5.89	0.162	2.17	0.59	7.98	0.242
67–100%	18	11	1.1	5.14	2.11	12.50	<0.001**	4.32	1.20	15.54	0.025*
Grade											
≤1	19	3	15.8	1							
2	49	16	32.7	2.30	0.67	7.89	0.186				
3	22	7	31.8	2.65	0.68	10.24	0.159				
Surgical margin (mm)											
>1	67	20	29.9	1							
≤1	23	6	26.1	0.84	0.34	2.10	0.713				
Lymphovascular invasion											
No	19	4	21.1	1							
Yes	71	22	31.0	1.59	0.55	4.60	0.397				
Extracapsular extension											
No	40	11	27.5	1							
Yes	50	15	30.0	1.07	0.49	2.33	0.868				
Tumor type											
ER/PR+ Her2–	50	15	30.0	1							
ER/PR+ Her2+	20	5	25.0	0.59	0.20	1.79	0.352				
ER/PR– Her2+	9	2	22.2	0.49	0.13	1.84	0.291				
TNBC	11	4	36.4	0.42	0.08	2.31	0.320				
Adjuvant chemotherapy or target therapy											
No	51	14	27.5	1							
Yes	39	12	30.8	1.29	0.60	2.79	0.519				

*, indicates P<0.05; **, indicates P<0.001. LRR, loco-regional recurrence; HR, hazard ratio; BCS, breast conserving surgery; LN+ ratio, positive ratio of dissected lymph nodes; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor type2; TNBC, triple negative breast cancer.

Table 3 Cox proportional-hazards regression analysis of relapse

Characteristics	Total	Relapse		Univariate analysis				Multivariate analysis (adjusted)			
		N	%	HR	95% CI		P value	HR	95% CI		P value
					Lower	Upper			Lower	Upper	
Age (years)											
≤50	53	23	43.4	1							
>50	37	18	48.6	1.13	0.827	1.543	0.445				
Surgery											
BCS	24	9	37.5	1							
Mastectomy	66	32	48.5	1.51	0.721	3.177	0.274				
Clinical stage											
c stage II	44	22	50.0	1							
c stage III	46	19	41.3	0.8	0.434	1.486	0.484				
Clinical T											
cT1–2	51	24	47.1	1							
cT3	24	11	45.8	0.84	0.409	1.708	0.622				
cT4	15	6	40.0	0.83	0.339	2.035	0.685				
Clinical N											
cN0	11	3	27.3	1				1			
cN1 micro/N1	57	26	45.6	2.13	0.636	7.113	0.22	3.97	1.08	14.51	0.037*
cN2	16	8	50.0	2.63	0.684	10.1	0.159	4.06	0.98	16.8	0.053***
cN3	6	4	66.7	6.73	1.457	31.11	0.015*	10.39	1.99	54.33	0.005*
Response											
Partial	52	18	34.6	1				1			
Stable	28	13	57.1	1.79	0.908	3.516	0.093	1.49	0.65	3.42	0.349
Progression	10	7	70.0	3.09	1.285	7.423	0.012*	3.73	1.42	9.83	0.008*
Pathological T											
T1–2	10	5	50.0	1							
T3	53	22	41.5	0.83	0.313	2.193	0.705				
T4	27	14	51.9	1.17	0.42	3.25	0.766				
Pathological N											
N0ihc/mi/1A	51	18	35.3	1				1			
N2a	29	16	55.2	1.75	0.89	3.433	0.105	1.07	0.46	2.49	0.867
N3a	10	7	70.0	2.72	1.131	6.554	0.025*	0.94	0.29	3.06	0.913
Dissected lymph node											
<10#	19	9	47.4	1							
≥10#	71	32	45.1	0.73	0.346	1.535	0.405				

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	Total	Relapse		Univariate analysis				Multivariate analysis (adjusted)			
		N	%	HR	95% CI		P value	HR	95% CI		P value
					Lower	Upper			Lower	Upper	
LN+ ratio											
0–33%	52	18	34.6	1				1			
34–66%	20	9	45.0	1.73	0.767	3.891	0.187	1.72	0.63	4.75	0.292
67–100%	18	14	77.8	3.65	1.789	7.444	< 0.001**	3.02	1.1	8.25	0.032*
Grade											
≤1	19	7	36.8	1							
2	49	23	46.9	1.56	0.658	3.714	0.312				
3	22	11	50.0	1.82	0.701	4.737	0.218				
Surgical margin (mm)											
>1	67	29	43.3	1							
≤1	23	12	52.2	1.19	0.607	2.332	0.613				
Lymphovascular invasion											
No	19	6	31.6	1							
Yes	71	35	49.3	1.68	0.707	4.00	0.239				
Extracapsular extension											
No	40	18	45.0	1							
Yes	50	23	46.0	0.98	0.528	1.819	0.949				
Tumor type											
ER/PR+ Her2–	50	24	48.0								
ER/PR+ Her2+	20	8	40.0	0.83	0.369	1.846	0.641				
ER/PR– Her2+	9	3	33.3	0.69	0.205	2.282	0.537				
TNBC	11	6	54.5	1.66	0.673	4.078	0.272				
Adjuvant chemotherapy or target therapy											
No	51	22	43.1	1							
Yes	39	19	48.7	1.26	0.681	2.329	0.462				

*, indicates P<0.05; **, indicates P<0.001; ***, indicates P close 0.05. LRR, loco-regional recurrence; HR, hazard ratio; BCS, breast conserving surgery; LN+ ratio, positive ratio of dissected lymph nodes; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor type2; TNBC, triple negative breast cancer.

Table 4 Cox proportional-hazards regression analysis of overall survival

Characteristics	Total	Death		Univariate analysis				Multivariate analysis (adjusted)			
		N	%	HR	95% CI		P value	HR	95% CI		P value
					Lower	Upper			Lower	Upper	
Age (years)											
≤50	53	13	24.5	1							
>50	37	10	27.0	1.10	0.73	1.66	0.652				
Surgery											
BCS	24	5	20.8	1							
Mastectomy	66	18	27.3	1.45	0.54	3.90	0.466				
Clinical stage											
c stage II	44	11	25.0	1							
c stage III	46	12	26.1	1.05	0.46	2.37	0.917				
Clinical T											
cT1–2	51	14	27.5	1							
cT3	24	5	20.8	0.68	0.24	1.89	0.456				
cT4	15	4	26.7	0.96	0.32	2.91	0.937				
Clinical N											
cN0	11	1	9.1	1				1			
cN1 micro/N1	57	14	24.6	3.14	0.41	23.99	0.271	2.90	0.38	22.51	0.308
cN2	16	5	31.3	4.76	0.55	41.03	0.156	4.56	0.52	40.40	0.172
cN3	6	3	50.0	10.73	1.09	106.14	0.042*	5.83	0.53	64.69	0.151
Response											
Partial	52	14	26.9	1							
Stable	28	5	17.9	0.68	0.24	1.88	0.457				
Progression	10	4	40.0	1.72	0.57	5.22	0.340				
Pathological T											
T1–2	10	4	40.0	1							
T3	53	12	22.6	0.55	0.18	1.70	0.299				
T4	27	7	25.9	0.67	0.20	2.29	0.523				
Pathological N											
N0ihc/mi/1A	51	11	21.6	1							
N2a	29	8	27.6	1.31	0.52	3.26	0.566				
N3a	10	4	40.0	2.33	0.74	7.35	0.150				
Dissected lymph node											
<10#	19	6	31.6	1							
≥10#	71	17	23.9	0.60	0.24	1.53	0.283				

Table 4 (*continued*)

Table 4 (*continued*)

Characteristics	Total	Death		Univariate analysis				Multivariate analysis (adjusted)			
		N	%	HR	95% CI		P value	HR	95% CI		P value
					Lower	Upper			Lower	Upper	
LN+ ratio											
0–33%	52	12	23.1	1							
34–66%	20	3	15.0	0.78	0.22	2.79	0.707				
67–100%	18	8	44.4	2.27	0.93	5.56	0.073				
Grade											
≤1	19	4	21.1	1							
2	49	13	26.5	1.39	0.45	4.25	0.570				
3	22	6	27.3	1.63	0.46	5.80	0.449				
Surgical margin (mm)											
>1	67	18	26.9	1							
≤1	23	5	21.7	0.80	0.30	2.17	0.665				
Lymphovascular invasion											
No	19	5	26.3	1							
Yes	71	18	25.4	1.05	0.39	2.82	0.929				
Extracapsular extension											
No	40	9	22.5	1							
Yes	50	14	28.0	1.22	0.53	2.83	0.636				
Tumor type											
ER/PR+ Her2−	50	12	24.0	1				1			
ER/PR+ Her2+	20	4	20.0	0.85	0.28	2.65	0.785	0.72	0.23	2.27	0.569
ER/PR− Her2+	9	1	11.1	0.46	0.06	3.57	0.461	0.49	0.06	3.78	0.49
TNBC	11	6	54.5	4.09	1.50	11.15	0.006*	3.04	1.01	9.16	0.048*
Adjuvant chemotherapy or target therapy											
No	51	11	21.6	1							
Yes	39	12	30.8	1.63	0.72	3.71	0.241				

*, indicates P<0.05. LRR, loco-regional recurrence; HR, hazard ratio; BCS, breast conserving surgery; LN+ ratio, positive ratio of dissected lymph nodes; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor type2; TNBC, triple negative breast cancer.

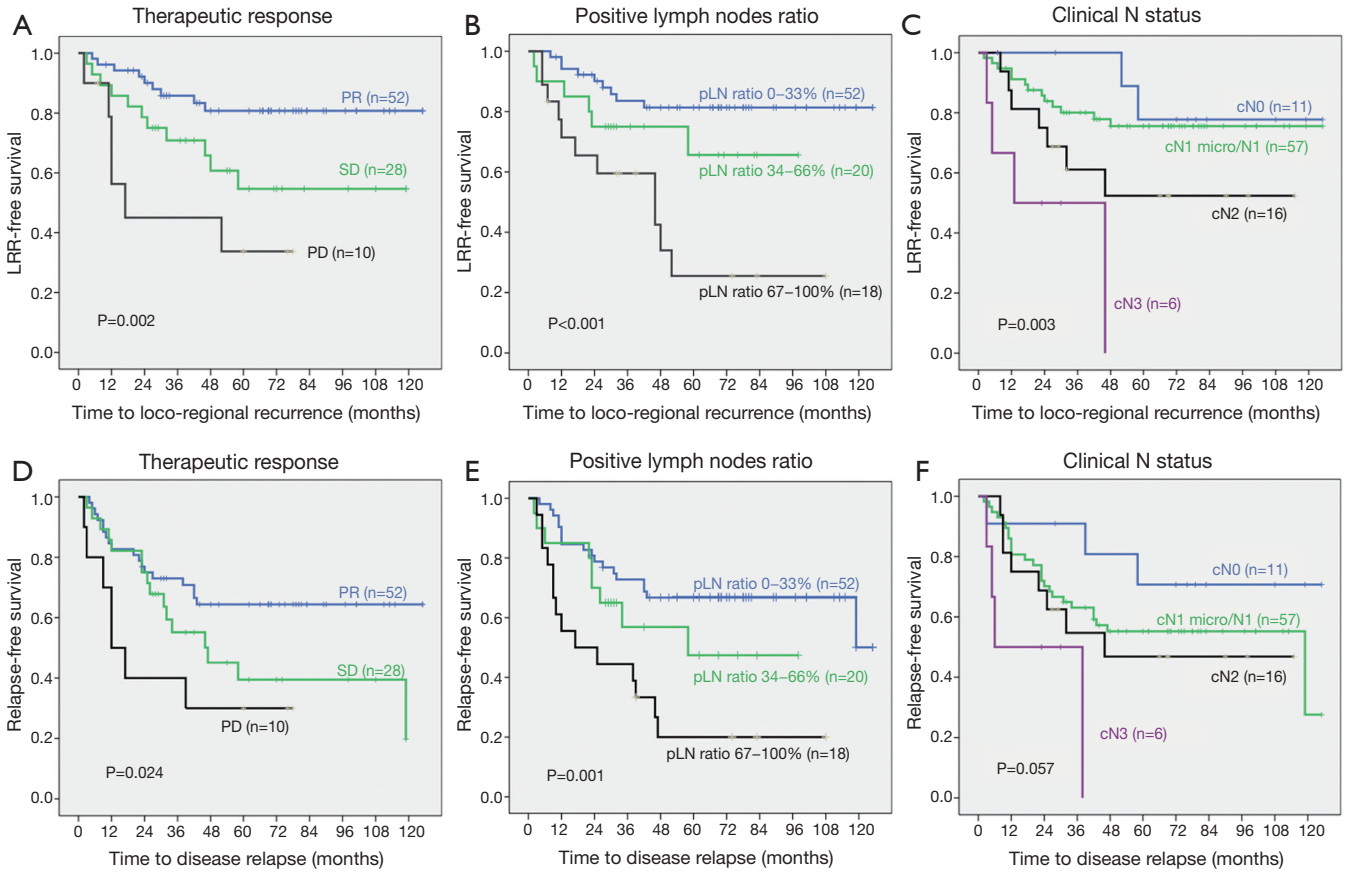

Figure 1 Loco-regional recurrence free survival and relapse free-survival by therapeutic response after neoadjuvant chemotherapy, positive lymph nodes ratio and clinical N status. (A) loco-regional recurrence-free survival by therapeutic response, P=0.002 by log-rank test; (B) loco-regional recurrence-free survival by positive lymph nodes ratio, P<0.001 by log-rank test; (C) loco-regional recurrence-free survival by clinical N status, P=0.003 by log-rank test; (D) relapse-free survival by therapeutic response, P=0.024 by log-rank test; (E) relapse-free survival by positive lymph nodes ratio, P=0.001 by log-rank test; (F) relapse-free survival by clinical N status, P=0.057 by log-rank test.

axillary dissection after NAC. For example, it has been reported that the lymphoid tissue in lymph nodes changed after NAC, including lymphoid depletion, fibrosis and hyalinization (1,22-24). In addition, the shrinkage of axillary lymph nodes after NAC allows surgeons to identify the lymph nodes in difficult scenarios and lessen the dissected volume during surgery (24-26). Moreover, the pathological examination skills (such as blunt dissection or fat dissolving technique and serial sectioning or radiological evaluation) affect the accuracy and resolution of tumor cell assessment in lymph nodes. Furthermore, different therapeutic responses after NAC act as important predictive factors. For instance, the number of dissected lymph nodes of <10 nodes may indicate a good response. Therefore, dissection <10 nodes cannot be considered as inadequate ALND in a typical NAC scenario. In this study, although the difference in the number of dissected lymph nodes of more than or less than 10 nodes was statistically significant in univariate analysis for LRR, it was not a risk factor in multivariate analysis and overlapped with the positive ratio of dissected nodes. Hence, in patients treated with NAC, the dissected number of lymph nodes >10 cannot predict prognosis similar to that in patients receiving primary surgery followed by adjuvant chemoradiation (non-NAC). Further studies related to this characteristic are required for clarity.

Positive lymph nodes ratio

Several studies in the past reported a positive lymph nodes ratio as a prognostic factor in patients treated primarily with surgery (non-NAC) (27-30). The positive lymph nodes ratio may be a better prognostic factor than the dissected lymph

nodes >10 nodes in patients with positive axillary nodes after NAC. Chen *et al.* reported that the positive lymph nodes ratio affects RFS and OS in patients with positive pathological lymph nodes after NAC. Moreover, they also found that, in patients with negative pathological lymph nodes after NAC, the total number of dissected lymph nodes (<10 nodes) affected RFS and OS (31). Wu *et al.* also revealed positive lymph nodes ratio as an independent prognostic factor of loco-regional control, distant metastasis (DM)-free survival, disease-free survival (DFS) and OS; however, ypN stage had no effect on prognosis (32). In the study by Cho *et al.*, it was reported that the positive lymph nodes ratio is significantly associated with DFS and OS. However, the pathologic N stage was not significantly associated with DFS and OS (33).

In this study, we also found that the positive lymph nodes ratio was associated with loco-regional control and relapse in axillary node-positive patients after NAC. Patients with 67–100% lymph nodes positive ratio showed greater LRR risk and relapse (HR =4.32 and P=0.025 and HR =3.02 and P=0.032, respectively). Thus, positive lymph nodes ratio may have more clinical significance than pathological lymph node status in patients receiving NAC.

Axillary recurrence

In patients receiving surgery primarily, a low proportion of patients in the early-stage showed axillary recurrence (0.2–2%) (19,34,35). A high rate of axillary recurrence (0.3–7%) was recorded only in early stage patients with positive lymph nodes identified by SLNB without further axillary treatment (36). In a 10-year report of NSABP B-18 and B-27 trials, patients treated with NAC and lumpectomy or mastectomy showed regional recurrence of 0–8.7% according to their therapeutic response (1). This study presented 90 patients with clinical stage II and III breast cancer with positive axillary lymph nodes after NAC, of which 26 patients had LRR and only 9 patients had axillary recurrence. Of the 9 patients with axillary recurrence, only 3 patients received irradiation to axillary level I region. Only few events were available to analyze the risks of axillary recurrence, we have presented the characteristics of patients with axillary recurrence in *Table 5*. There was obviously a trend that patients with primary tumor in the upper-outer quadrant and those with extracapsular extension of lymph nodes tended to have axillary recurrence. In addition, 6 of 9 patients had lymph nodes positive ratio >50%. LRR rate was higher in our study than that shown in NSABP B18 and B27 (LRR: 0–8.7%), which was possible only because we included patients with positive lymph nodes after NAC [NSABP analysis data including negative axillary lymph nodes (ypN0) after NAC]. In the NSABP studies, no patients with clinical N2/N3 status (stage III) and >50% patients with cT1–2N0 (stage IA/IIA) in NSABP B18 (65%) and B27 (51%) were recorded. Only patients with clinical stages II and III breast cancer were enrolled in this study and this population presented with higher risks of LRR.

In non-NAC situations, the study by Kaygusuz *et al.* revealed the presence of extracapsular extension indicates more advanced axillary disease and is associated with higher DM rate (37). Another study showed the presence of extracapsular extension in association with higher recurrence and mortality rate (38) and the perpendicular diameter of extra-nodal growth (>3 mm) affected DFS and cancer-specific survival (39). In patients treated using NAC, the presence of extracapsular extension could also predict the DFS. There was no evidence showing that the presence of extracapsular extension can contribute to regional recurrence. However, the axillary recurrence in this study seems to be associated with the presence of extracapsular extension and tumor located in the upper-outer quadrant. Further studies are required to investigate these factors to design the optimal radiation treatment field, particularly for those patients with only SLNB or inadequate ALND.

Biomarker/molecular type

According to the MSKCC retrospective data (40), patients with TNBC showed the highest LRR after NAC, mastectomy, and PMRT; TNBC patients with residual disease after NAC showed greater risk for LRR than patients with pCR. However, this study included only 11 (12%) patients with TNBC, which made correlation analysis difficult. Assessment of the molecular type was an accurate predictor of survival in patients treated with NAC (41-44). Patients with HER2 positive showed good response to NAC with target therapy and easily achieved pCR. Of the common molecule types, the prognosis of patients with HER2 positive type was most related to pCR (6).

In this study, 2 of 9 patients (22.2%) had ER(–)/PR(–)/HER2(+) and 4 of 11 TNBC patients (36.4%) had LRR; only 3 of 9 patients (33.3%) with ER(–)/PR(–)/HER2(+) and 6 of 11 patients with TNBC (54.5%) had DM. Although the limited number cases could not show statistical significance, Herceptin-application may improve disease control in patients with HER2 positive results, as

Table 5 Characteristics of 9 patients with axillary lymph nodes recurrence in this cohort study

Case No.	Age at diagnosis	Operation method	Clinical T/N	Pathological T/N	Response after NAC	LN+ ratio group	LN+ ratio	Number of dissected lymph nodes	Tumor location	ECE	Level I RT
1	59	Total mastectomy	cT2N1	ypT2N3a	SD	67–100%	68.8%	16	Upper and LOQ[§]	+	–
2	56	Total mastectomy	cT2N1	ypT1aN3a	PR	67–100%	100.0%	11	UOQ	+	+
3	57	BCS	cT1cN2	ypT1cN1mi	SD	67–100%	75.0%	4	UIQ	–	–
4	49	Total mastectomy	cT3N1	ypT3N3a	SD	67–100%	100.0%	13	UOQ	–	–
5	57	BCS	cT2N2	ypT1cN1a	PR	34–66%	50.0%	4	Central	+	+
6	35	Total mastectomy	cT4bN3	ypT4bN2a	SD	34–66%	46.7%	15	UOQ	+	–
7	47	BCS	cT2N1	ypT2N2a	SD	34–66%	60.0%	10	UOQ	–	–
8	66	Total mastectomy	cT2N1	ypT2N1a	PD	34–66%	42.9%	7	UIQ	–	+
9	54	Total mastectomy	cT2N1	ypT3N1a	PD	1–33%	11.1%	9	UOQ	+	–

Characteristics of 9 patients with axillary lymph nodes recurrence in this cohort study showed 6 (66.7%) patients had positive ratio of dissected lymph nodes >50%, 6 (66.7%) patients had primary tumor at upper outer quadrant or 12 o'clock and 5 (55.6%) patients had lymph nodes metastasis with extracapsular extension. [§], two separate tumors at 2 cm from areolar border at 12 o'clock and 3 cm from areolar border at 8 o'clock. BCS, breast conserving surgery; NAC, neoadjuvant chemotherapy; LN+, lymph node positive; ECE, extracapsular extension; RT, radiotherapy; PR, partial response; SD, stable disease; PD, progressive disease; UIQ, upper inner quadrant; UOQ, upper outer quadrant; LOQ, lower outer quadrant.

shown in patients with ER(–)/PR(–)/HER2(+) and TNBC in this study. However, we only found that the TNBC type showed statistical significance in the uni-/multi-variate analysis for OS, which could be due to the small number of enrolled patients and the relatively short-term follow-up duration.

This study included patients with pathologically positive lymph nodes. Exclusion of patients with pCR (ypTis/T0 N0) decreased the strong impact of therapeutic response on other risk factors independent of achieving statistical significance. Univariate and multivariate analyses revealed that therapeutic response, clinical N status, and positive lymph nodes ratio were risk factors of LRR and DM. Several studies have showed therapeutic response (41-43), clinical N status (45,46) and positive ratio of dissected LN (31-33) as predictors of disease control. However, the risk factors found by these studies, such as grade 3 (47), presence of lymphovascular invasion (45-47), ypN2–3 (47), primary tumor size (45-47), pathologic tumor size after NAC (46), age (1), molecular type (TNBC) (6,40), and positive surgical margin (48) failed to achieve any statistical significance or trends as shown in other studies. It may be attributed to the relatively fewer number of cases and events, short follow-up period, and selection bias which are the inherent features of a retrospective study.

The pathological lymph nodes status, such as ypN1 and ypN2 in NAC scenarios was not obviously significant in predicting disease control as in non-NAC scenarios, both in the present study and others NAC studies. This prognostic factor may be interfered by NAC. Whether positive lymph node ratio is a better prognostic factor than only the number of positive lymph nodes requires further detailed investigation.

In non-NAC scenarios, the number of positive axillary lymph nodes and dissected lymph nodes can be used to determine the loco-regional treatment such as radiotherapy indication and field-design (axillary irradiation) after primary surgery. However, in NAC scenarios, the predictive value of both the factors would be affected by several reasons such as therapeutic response after NAC,

lymphoid depletion in axillary nodes after NAC, decreasing dissected volume of ALND, and pathological techniques. In this study, positive lymph nodes ratio seemed to be more valuable for prognosis than the number of positive axillary lymph nodes and dissected lymph nodes. Despite insufficient evidence, irradiation to axillary level I region could be considered when ypN+ patients present with high positive ratio and low number of dissected lymph nodes.

This study has some limitations. First, it is a retrospective study and therefore includes some bias. Longer follow-up period and a larger sample size in the future studies will help provide better result for breast cancer study. In response, the Alliance 011202 trial phase-III randomized trial, including clinical T1–3N1M0 patients with positive axillary lymph nodes after NAC, has been initiated to address the question about axillary recurrent risks and their management.

Conclusions

The consensus on the exact role of radiotherapy in the management of patients with breast cancer undergoing NAC with regard to the therapeutic response remains unclear. In this study, we recorded poor therapeutic response, advanced clinically positive lymph nodes, and higher proportional positivity of dissected lymph nodes showing poor outcome regarding to the loco-regional control and RFS among patients with positive axillary lymph nodes after NAC. The decision whether radiotherapy can be delivered to the regional lymphatic areas, including axilla, should depend on the chemotherapeutic response and surgical extent, particularly in patients with incomplete response of the lymph nodes with high positive lymph nodes ratio. Future prospective studies will provide us with more accurate risk predictors of LRR for better planning of the treatment design.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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