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Original Article

Prognostic significance of lymph node metastasis in triple negative ductal carcinoma of the breast: a retrospective cohort study

Hongliang Chen, Ang Ding, Maoli Wang, Chuyang Yin, Zheng Zhang

Department of Breast Surgery, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China

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Abstract: Objective: The purpose of this study was to identify the prognostic significance of lymph node (LN) metastasis in triple negative breast cancer (TNBC). Methods: A retrospective analysis of 206 TNBC was conducted. Clinicopathological characteristics between different LN statuses were compared by *Chi*-square test. Survival differences among pT stages, pN stages, lymphovascular invasion (LVI) etc. were compared by Log-rank test. All variables with statistical significance in the univariate analysis were investigated in multivariate analysis by COX regression. Results: The mean age of 206 TNBC patients was 49.80 ± 10.06 years old. The mean size of tumor was 2.96 ± 2.01 cm. There were altogether 83 cases (40.3%) with positive LNs, among which 50 cases in pN1 stage, 24 cases in pN2 stage and 9 cases in pN3 stage. Tumor size and LVI were correlated with LN metastasis. Tumor size (P = 0.023 for DFS, 0.012 for OS), LVI (P = 0.001 for DFS, 0.003 for OS) and LN status (negative or positive) (P = 0.017 for DFS, 0.008 for OS) rather than pN stage (P = 0.090 for DFS, 0.061 for OS) were independent prognostic factors of TNBC. There were no statistically significant differences in the prognosis among pN1-pN3 regardless of tumor size or LVI status. Conclusions: For TNBC, LN status was an independent prognostic factor. But for cases with LN metastasis, the prognosis was not greatly affected by the number of positive LNs. Perhaps apart from lymphatic metastasis, hematogenous metastasis played an important role in TNBC progression, even at an early stage.

Keywords: Triple negative breast cancer, lymph node metastasis, prognosis

Introduction

Currently, breast cancer is the most common cancer among women worldwide. Axillary lymph node (LN) metastasis is one of the most important prognostic factors for the survival of breast cancer [1, 2]. The 5-year disease-free survival (DFS) for breast cancer patients with LN metastasis is 40%, lower than that of patients without LN metastasis [3].

With the advances in molecular biology and microarray analysis, breast cancer can be segregated into different "intrinsic subtypes", which enhanced our understanding of breast cancer heterogeneity. Different molecular subtypes have distinct biological behavior, suggesting that molecular subtype has important value in comprehensive evaluation of prognosis [4].

Triple negative breast cancer (TNBC) is defined by the lack of expression of the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), which accounts for 15-20% of breast cancer patients. It is the most aggressive subtype of invasive ductal carcinoma of the breast (IDC), characterized by occurrence at young age, early relapse especially visceral metastasis, and lack of targeted therapy [5, 6]. Most studies consider the TNBC subtype as an independent marker of a poor prognosis [7-9].

In spite of poor prognosis, TNBC is not associated with increased likelihood of LN metastases. Gangi A *et al.* pointed out that patients with TNBC are not more likely to have involved nodes than those with non-TNBC [10]. And early distant metastasis can be observed at relatively high frequency in TNBC patients with negative LN or few positive LNs.

Although TNBC subtype and LN metastasis have both been independently demonstrated as prognostic factors, there is little data focusing on the prognostic significance of LN metas-

Table 1. Clinicopathological characteristics according to lymph node status

	Lymph node negative Cases (%)	Lymph node positive Cases (%)	*P* value
Menopause status			0.133
Pre-menopausal	61 (49.6%)	50 (60.2%)	
Post-menopausal	62 (50.4%)	33 (39.8%)	
Histological grade			0.503
Median	41 (33.3%)	24 (28.9%)	
low	82 (66.7%)	59 (71.1%)	
Tumor size			0.002
≤ 2 cm	56 (45.5%)	20 (24.1%)	
> 2 cm	67 (54.5%)	63 (75.9%)	
LVI			< 0.001
Negative	91 (74.0%)	41 (49.4%)	
Positive	32 (26.0%)	42 (50.6%)	
Surgery			0.752
Mastectomy	87 (70.7%)	57 (68.7%)	
BCS	36 (29.3%)	26 (31.3%)	
Chemotherapy			0.617
Adjuvant	97 (78.9%)	63 (75.9%)	
neoadjuvant	26 (21.1%)	20 (24.1%)	

tasis on TNBC patients. Therefore, we conducted an extensive retrospective study to provide a more complete overview of the subject.

Patients and methods

A retrospective study was conducted, in which 206 breast cancer patients in TNBC-IDC subtype treated in Obstetrics and Gynecology Hospital of Fudan University between June 2007 and June 2014 were enrolled. Patients were excluded for the following reasons: male gender, in situ lesion, curative resection was not conducted or distant metastasis was confirmed before surgery.

The baseline data included demographic characteristics (e.g., age, menopause), and tumor characteristics (e.g., tumor size stage, LN stage, lymphovascular invasion (LVI), histologic grade). Tumor size and LN staging in this study was based on the AJCC Staging 7th edition [11]. All patients received mastectomy or breast-conserving surgery (BCS) plus axillary LN dissection/sentinel LN biopsy, adjuvant/neoadjuvant chemotherapy composed anthracycline and/or taxane followed by radiotherapy (if required).

The status of the ER, PR, and HER2 were determined by immunohistochemical (IHC) staining. The cut-off value for ER positivity and PR positivity was 1% of tumor cells with positive nuclear staining. Tumors with an IHC score of 3+ based on circumferential membrane-bound staining or with amplification confirmed by florescent in situ hybridization (FISH) were defined as HER2-positive. Tumors with an IHC score of 2+ were recommended FISH test.

Follow-up information regarding tumor relapse and survival status was available through outpatient departmental records and personal contact with the patients via mail and telephone calls until June 2015. The follow-up duration was calculated from the date of diagnosis until the date of death or last contact. Disease-free survival (DFS) was the time between diagnosis and confirmation of disease relapse. Overall survival (OS) was the time between diagnosis and death as a result of any cause. Those without any evidence of relapse or lost to follow-up were censored at the date of their last follow-up.

Statistical analyses

Data were expressed as mean ± standard deviation (SD) for continuous variables. Categorical variables were normally tested with *Chi*-square test (Pearson statistic) when appropriate. Survival curves were constructed using the Kaplan-Meier method, and univariate survival difference was determined with the log-rank test. All variables with statistical significance in the univariate analysis were investigated by multivariate analysis. Adjusted hazard ratios (HRs) with 95% confidence intervals (95% CI) were calculated using Cox proportional hazards model. All the statistical analysis was performed using SPSS 19.0 software package (SPSS, Chicago, IL, USA). Two-sided $P < 0.05$ was considered statistically significant.

Results

Clinicopathologic characteristics according to lymph node status

The mean age of 206 TNBC patients was 49.80 ± 10.06 years old (range 22-70). The mean size of tumor was 2.96 ± 2.01 cm (range 1.0-15.0).

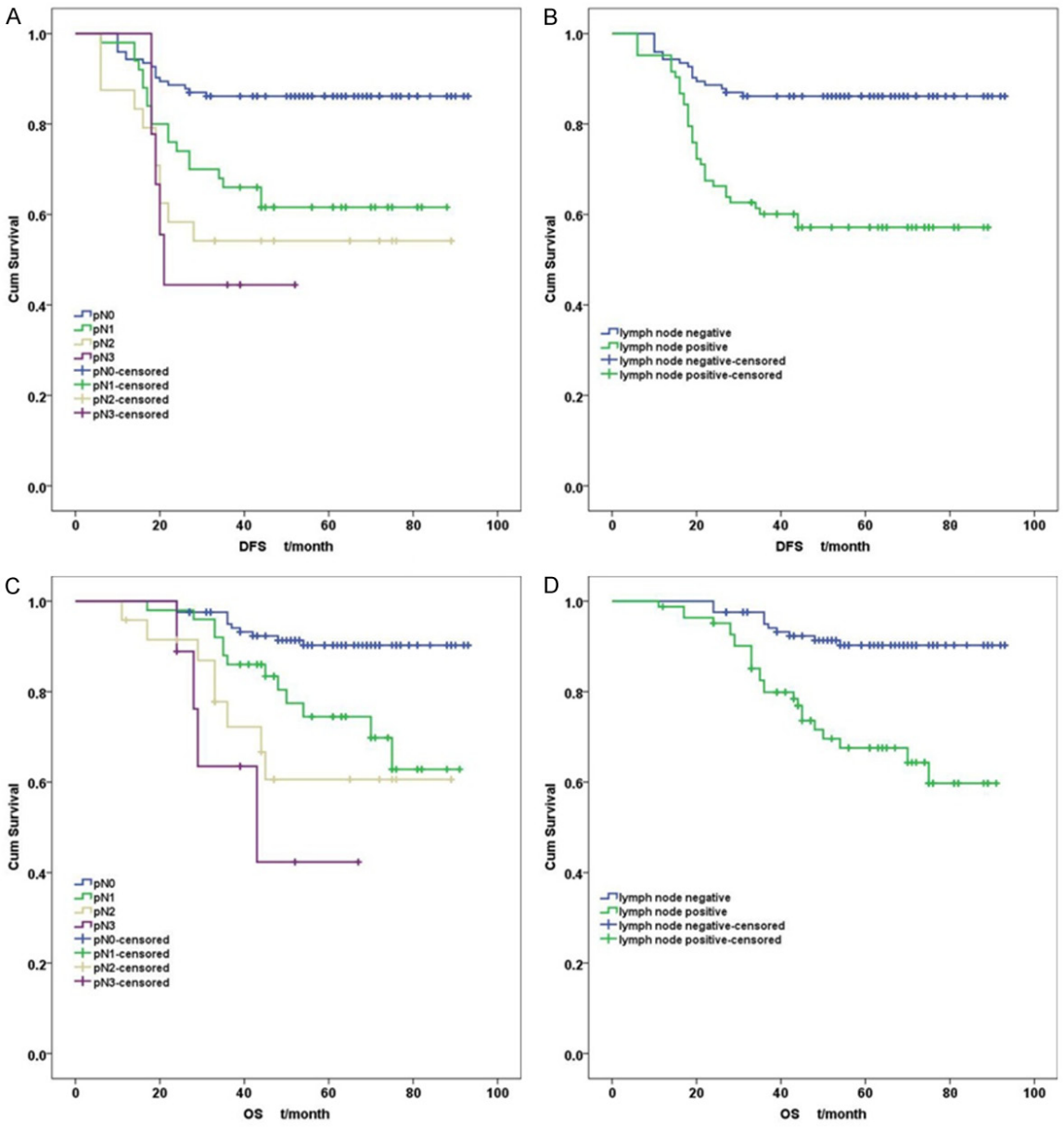


Figure 1. Survival curves according to pN stage and LN status. A. DFS according to pN stage; B. DFS according to LN status; C. OS according to pN stage; D. OS according to LN status.

There were 76 cases in T1 stage, 112 cases in T2 stage, and 18 cases in T3 stage. There were altogether 83 cases (40.3%) with positive LNs, among which 50 cases in pN1 stage, 24 cases in pN2 stage and 9 cases in pN3 stage. The median number of positive LNs was 2 (range 1-24). The mean number of LNs removed was 15.96 ± 5.04 (range 8-35). Median follow-up duration was 58 months (range 8-96). 5-year DFS rate was 75.6% and 5-year OS rate was 85.1%.

The clinicopathologic characteristics according to LN status were summarized in **Table 1**. It was shown that the tumor size and LVI were correlated with LN status. Tumor size > 2 cm ($P = 0.002$) and positive LVI ($P < 0.001$) were more likely to be observed in cases with positive LNs.

Univariate analysis of possible factors correlated with prognosis

Univariate analysis by Log-rank test revealed that larger tumor size ($P < 0.001$ for DFS and OS), higher pN stage ($P < 0.001$ for DFS and OS) (**Figure 1A**, **1C**), and positive LVI ($P < 0.001$ for DFS and OS) were correlated with decreased DFS and OS. And menopause status ($P = 0.185$

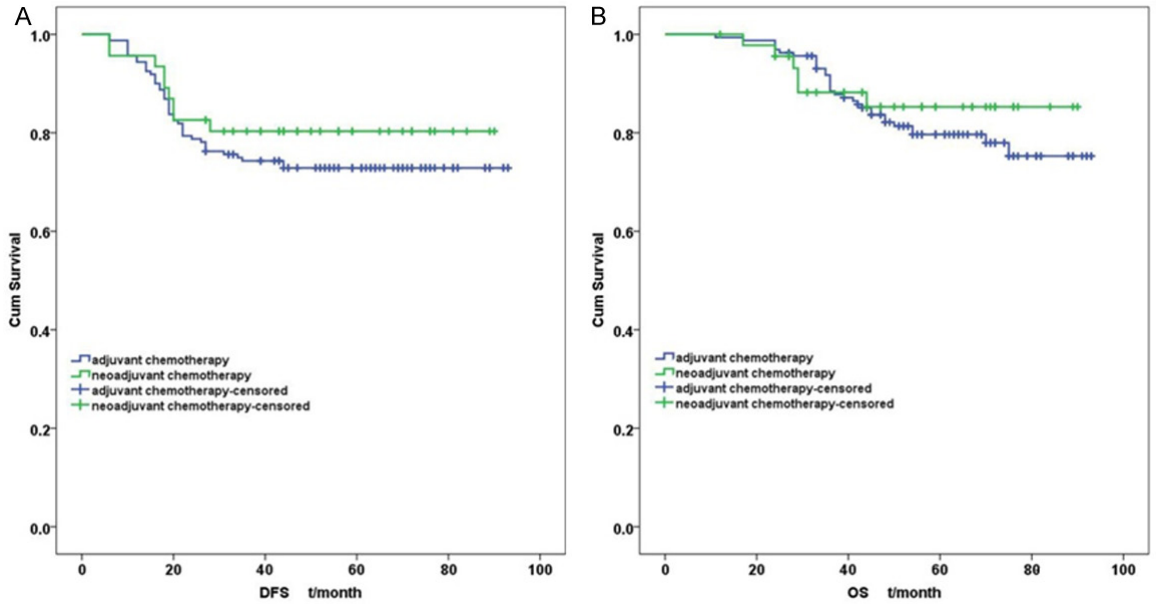


Figure 2. Survival curves according to chemotherapy mode. A. DFS according to chemotherapy mode; B. OS according to chemotherapy mode.

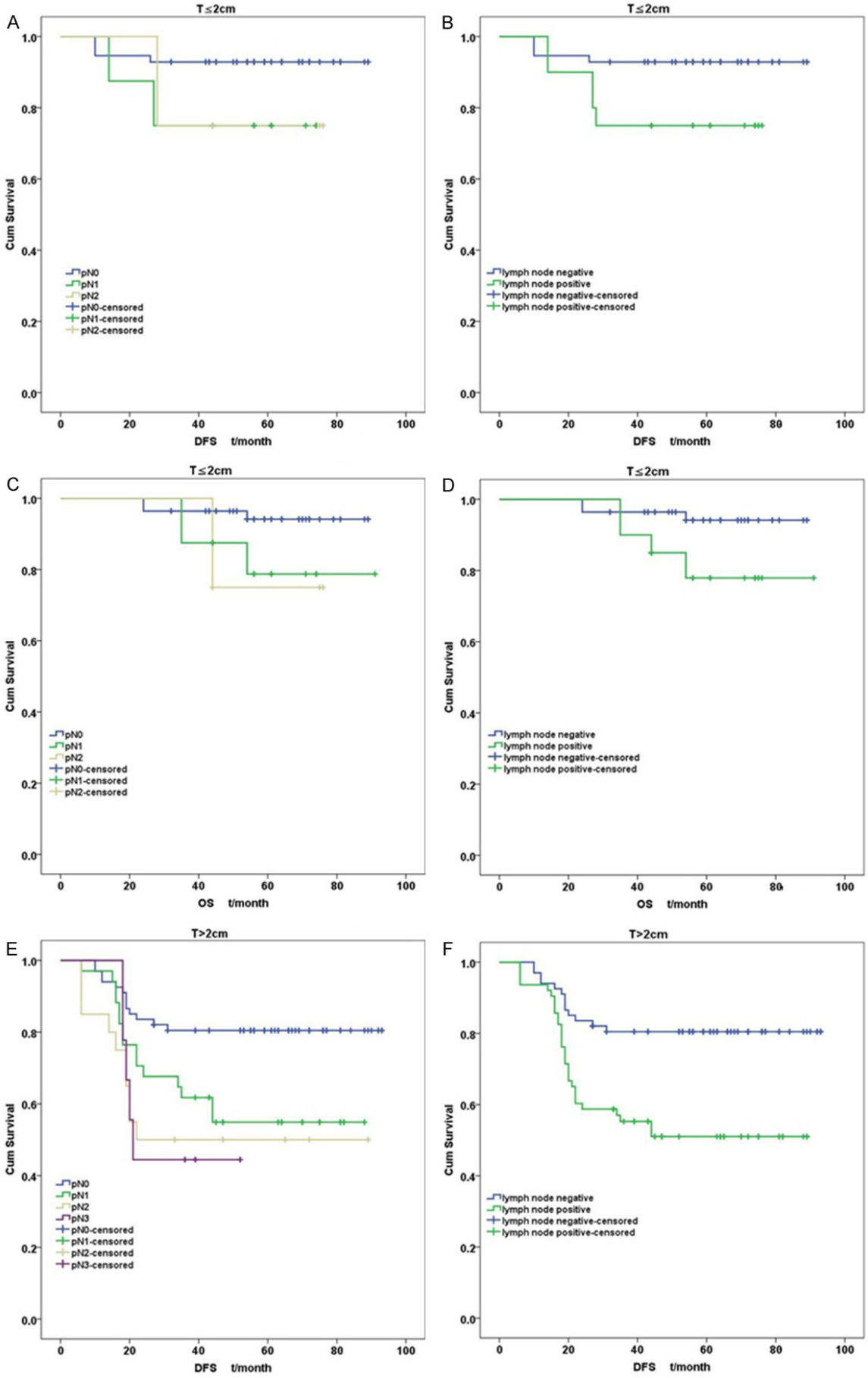
for DFS, 0.494 for OS), histologic grade (P = 0.909 for DFS, 0.609 for OS), surgery mode (P = 0.589 for DFS, 0.331 for OS) and chemotherapy mode (P = 0.354 for DFS, 0.539 for OS) were not correlated with prognosis.

Further analysis showed that there was a statistically significant separation between the Kaplan-Meier survival curves of LN statuses (P < 0.001 for DFS and OS) (**Figure 1B**, **1D**) rather than of pN1-pN3 (P = 0.443 for DFS, 0.091 for OS).

There was a trend of DFS and OS benefit in patients receiving neoadjuvant chemotherapy compared with those receiving adjuvant chemotherapy, although it did not reach statistical significance. (P = 0.354 for DFS, 0.539 for OS) (**Figure 2**).

As tumor size was correlated with LN status (**Table 1**), survival analysis was conducted according to LN stage in tumor size ≤ 2 cm and tumor size > 2 cm respectively (**Figure 3**). Among cases in tumor size ≤ 2 cm, none was in pN3 stage. For cases with tumor size ≤ 2 cm, pN stage was not correlated with DFS (P = 0.125) or OS (P = 0.145) (**Figure 3A**, **3C**). Further analysis showed that there was a statistically significant difference between the Kaplan-Meier survival curves of LN status (P = 0.045 for DFS, 0.042 for OS) (**Figure 3B**, **3D**) rather than of pN1-pN2 (P = 0.917 for DFS, 0.788 for OS). For cases with tumor size > 2 cm, pN stage was correlated with DFS (P = 0.006) and OS (P = 0.002) (**Figure 3E**, **3G**). Further analysis showed that there was a statistically significant difference between the Kaplan-Meier survival curves of LN status (P = 0.001 for DFS, 0.002 for OS) (**Figure 3F**, **3H**) rather than of pN1-pN3 (P = 0.641 for DFS, 0.187 for OS).

As LVI status was also correlated with LN status (**Table 1**), survival analysis was conducted according to LN stage in positive or negative LVI respectively (**Figure 4**). Among cases with negative LVI, none was in pN3 stage. For cases with negative LVI, pN stage was correlated with DFS (P < 0.001) and OS (P = 0.003) (**Figure 4A**, **4C**). Further analysis showed that there was a statistically significant difference between the Kaplan-Meier survival curves of LN status (P < 0.001 for DFS, 0.005 for OS) (**Figure 4B**, **4D**) rather than of pN1-pN2 (P =0.216 for DFS, 0.211 for OS). For cases with positive LVI, pN stage was not correlated with DFS (P = 0.288) or OS (P = 0.083) (**Figure 4E**, **4G**). Further analysis showed that there was a statistically significant difference between the Kaplan-Meier survival curves of LN status (P = 0.046 for DFS, 0.016 for OS) (**Figure 4F**, **4H**) rather than of pN1-pN3 (P = 0.947 for DFS, 0.652 for OS).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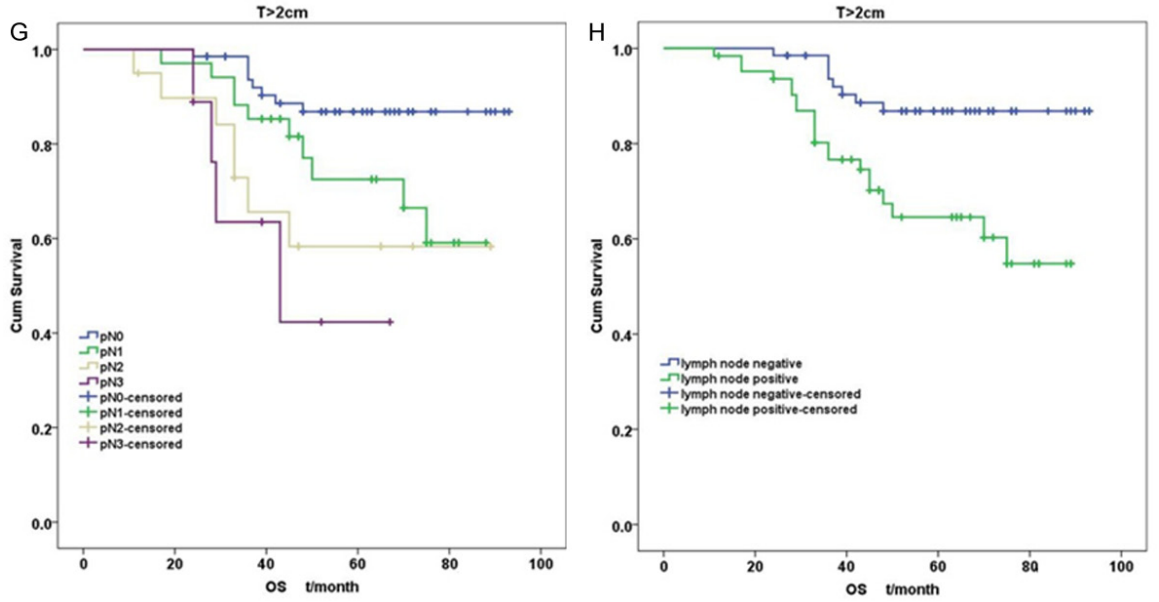


Figure 3. Survival curves according to pN stage and LN status in different tumor size layer. A. DFS according to pN stage in tumor ≤ 2 cm; B. DFS according to LN status in tumor ≤ 2 cm; C. OS according to pN stage in tumor ≤ 2 cm; D. OS according to LN status in tumor ≤ 2 cm; E. DFS according to pN stage in tumor > 2 cm; F. DFS according to LN status in tumor >2 cm; G. OS according to pN stage in tumor > 2 cm; H. OS according to LN status in tumor > 2 cm.

From above, it could be concluded that for TNBC the prognosis was affected greatly by LN status. But for cases with positive LNs, the prognosis was not greatly affected by the number of positive LNs.

Multivariate analysis of prognostic factors for TNBC

When pT, pN and LVI were entered into the Cox proportional hazards model as covariates, pT and LVI were both independent prognostic factors of DFS (pT: P = 0.017, LVI: P = 0.001) and OS (pT: P = 0.018, LVI: P = 0.002), but pN was not an independent prognostic factor for DFS or OS (P = 0.090 for DFS, 0.061 for OS).

When pT, LN status and LVI were entered into the Cox proportional hazards model as covariates, they were all independent prognostic factors of DFS and OS (**Table 2**).

So for TNBC, LN status rather than pN stage was the prognostic factor. For cases with positive LNs, the survival rate did not decrease linearly with the increase of positive LNs.

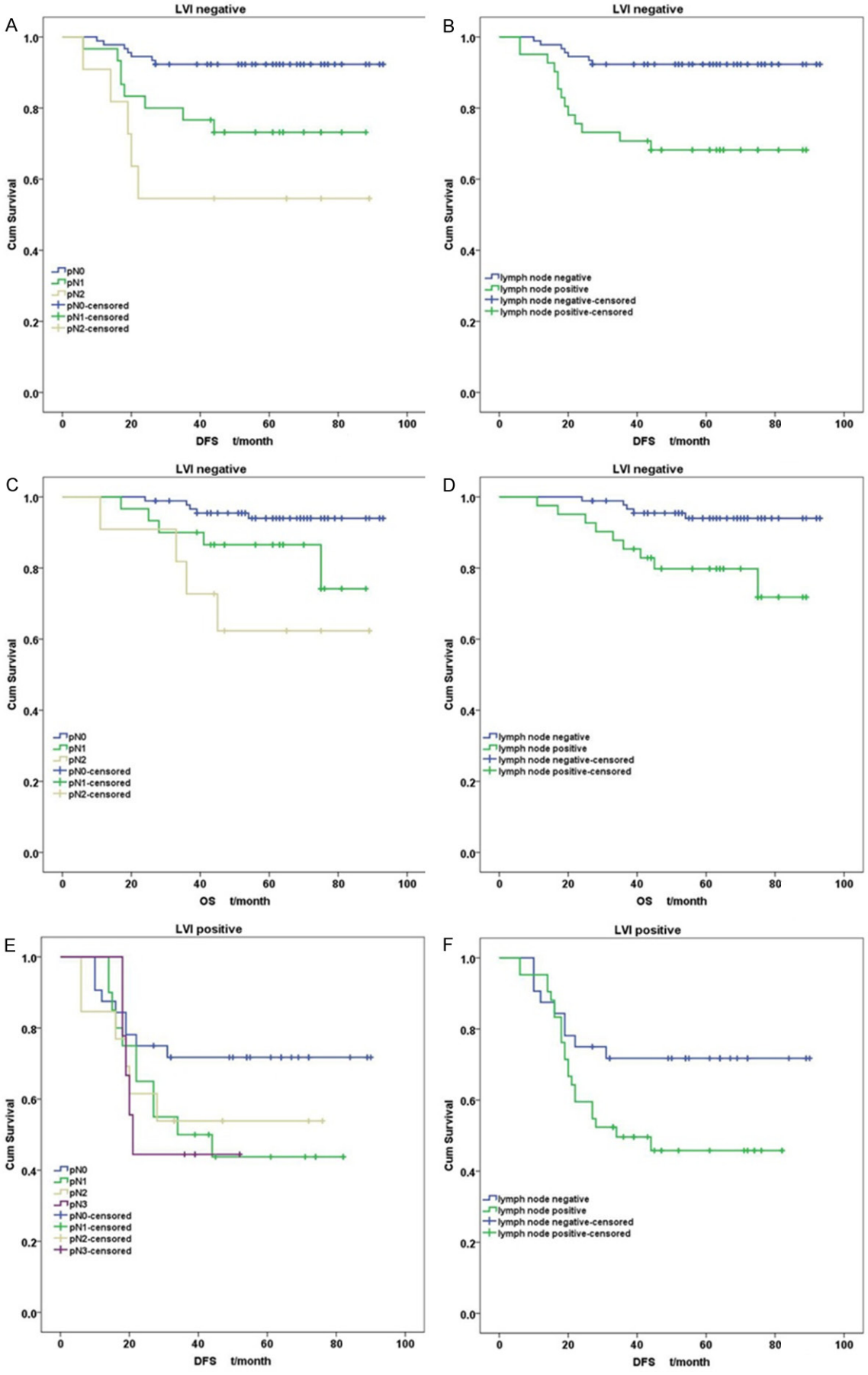
Discussion

The poor prognosis of TNBC may be due to a higher propensity for distant (rather than regional) spread [12, 13]. Research into the prognostic factors of TNBC may help to instruct the clinical practice and pave the way for mechanism study.

The 7th edition of staging in breast cancer has included tumor size and LN status as the most important prognostic factors [11]. The size of the primary tumor and the number of positive lymph nodes has an inverse linear relationship with prognosis and survival [14]. But for TNBC, it is not always the same case.

Some recent publications have suggested the role of molecular subtypes in the risk of LN involvement [15-17]. Although its poor survival compared with other subtypes, TNBC did not demonstrate the highest extent of LN involvement [15, 16]. Greater probability of LN involvement was in the luminal B and luminal HER2 subtypes [2, 18]. It was reported that the LN metastasis rate in TNBC was 25-54% [2, 18-20]. In our cohort, the rate was 40.3%, and 60% were in pN1 stage, which was in accord with the literature [9].

Our study revealed that the prognosis was poorer in cases with positive LN than in negative LN, regardless of tumor size or LVI status.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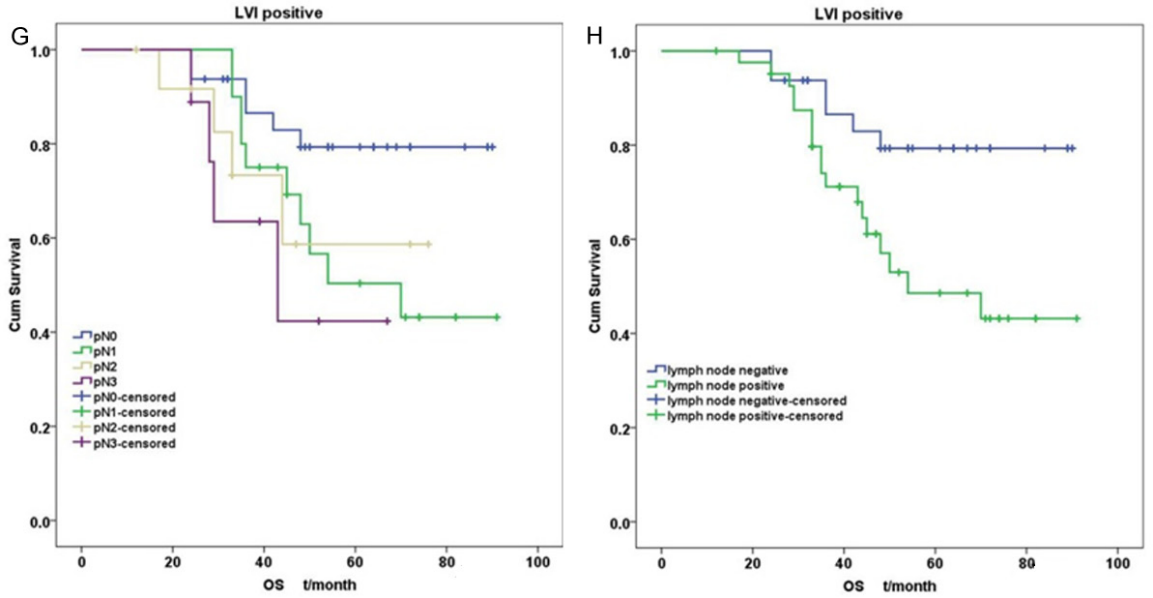

Figure 4. Survival curves according to pN stage and LN status in different tumor LVI status layer. A. DFS according to pN stage in negative LVI; B. DFS according to LN status in negative LVI; C. OS according to pN stage in negative LVI; D. OS according to LN status in negative LVI; E. DFS according to pN stage in positive LVI; F. DFS according to LN status in positive LVI; G. OS according to pN stage in positive LVI; H. OS according to LN status in positive LVI.

Table 2. Multivariate analysis of prognostic factors of TNBC

	DFS			OS		
	HR	*P* value	95% CI	HR	*P* value	95% CI
pT		0.023			0.012	
T2:T1	2.604	0.013	1.228-5.522	2.325	0.057	0.974-5.551
T3:T1	3.351	0.013	1.292-8.693		0.003	1.684-12.932
Lymph node status						
Positive:negative	2.148	0.017	1.146-4.025	2.741	0.008	1.301-5.774
LVI						
Positive:negative	2.708	0.001	1.486-4.936	2.939	0.003	1.453-5.945

But in cases with positive LN, the survival rate did not decrease linearly with the upgrading of pN stage, regardless of tumor size or LVI status, either. As the prognosis was not greatly affected by the number of additional positive LNs, TNBC had a distinct biologic behavior that differed from other subtypes in which the number of positive LNs correlated with prognosis [3, 21]. So Park *et al.* concluded that in TNBC, the AJCC TNM staging system was not discriminative to reflect the survival rate as the other subtypes [22].

Our study showed that LVI was an independent prognostic factor, although it correlated with positive LN status, suggesting that apart from lymphatic metastasis, hematogenous metastasis played an important role in TNBC progression, even at an early stage. Liu *et al.* demonstrated higher levels of intratumoral and peritumoral lymphangiogenesis in early stages of TNBC. Patients with early LN involvement may already have distant metastasis [23]. This may partly explain our study's result that the prognosis was not affected by the increase of positive LNs.

It was reported that TNBC was associated with a larger tumor size [20]. In our study, 63.1% cases had a tumor size over 2 cm. Our study also demonstrated that larger tumor size occurred more frequently in cases with positive LNs, and it was in accord with Hernandez-Aya's research which confirmed the relationship through a review of 1711 TNBC patients [19]. Multiple studies indicated that tumor size was important for predicting LN metastasis [24].

In our study, tumor size was an independent prognostic factor, which agreed with Anders's report [25]. Although larger tumor correlated

with positive LN, it was tumor size rather than positive pN stage that was the independent prognostic factor. Combined with the importance of hematogenous metastasis in TNBC, we hypothesized that tumor cells of TNBC may be more likely to detach from larger mass to migrate to distant site through circulation to form a new metastasis.

The result of our study has important clinical significance. More attention should be paid to the systemic treatment of early micrometastasis through circulation rather than extensive local treatment. Neoadjuvant chemotherapy provides the earliest chance to treat micrometastatic disease, saving time that could potentially be lost to local treatment. And neoadjuvant chemotherapy may enhance the local effect through the intact neovasculature associated with cancer which could have been altered by surgical excision [26]. Our study showed a tendency of improved survival favoring neoadjuvant chemotherapy although without statistical significance, possibly due to small sample size of cases receiving neoadjuvant chemotherapy. Meanwhile BCS had no adverse influence on survival, which was in accord with the literature [27]. Therefore neoadjuvant chemotherapy and BCS should be recommended for suitable TNBC patients.

Some limitations of this study should be acknowledged. First, selection bias was not completely avoided because this was a retrospective cohort study. Furthermore, Ki-67 pathological data were not routinely obtained from patients, but it may have an effect on survival.

In conclusion, our study indicated that in TNBC, tumor size and LVI correlated with LN status. Tumor size, LVI, and LN status were all independent prognostic factors. But once there was any evidence of LN involvement, the survival rate did not decrease linearly with the upgrading of pN stage, regardless of tumor size or LVI status. Further researches are warranted for the mechanisms of this aggressive behavior.

Disclosure of conflict of interest

None.

Address correspondence to: Hongliang Chen, Department of Breast Surgery, Obstetrics and Gynecology Hospital of Fudan University, 419 Fangxie Road, Huangpu District, Shanghai 200011, China. E-mail: hongliangchen1982@163.com

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