

Prognostic analysis of triple-negative breast cancer patients treated with adjuvant chemotherapy of fluorouracil, epirubicin and cyclophosphamide

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Abstract. The aim of the present study was to investigate the association between the clinicopathological and demographic factors, and the survival time of patients with triple-negative breast cancer (TNBC) in China. The patients had received adjuvant chemotherapy consisting of 5-fluorouracil, epirubicin and cyclophosphamide (FEC; 500 mg/m² cyclophosphamide, day 1; 75 mg/m² epirubicin, day 1; 500 mg/m² 5-fluorouracil, days 1 and 8; every 3 weeks, for at least 4 cycles). The clinicopathological and demographic factors affecting the outcome of the patients with TNBC that received adjuvant FEC chemotherapy were evaluated. Within these variables, the overall survival (OS) and disease-free survival (DFS) times were analyzed using the log-rank test, which was constructed using the multivariate Cox proportional hazards regression model and Kaplan-Meier analysis. Additionally, Spearman's χ^2 test was used to analyze categorical variables. In the univariate statistical analysis, the significant risk factors for TNBC patient survival were the stage of disease and lymph node status, which were associated with the OS and DFS, and the total number of pregnancies, which was associated with the DFS. In the multivariate Cox proportional hazard model, lymph node status was an independent prognostic indicator of OS

[P<0.001; hazard ratio (HR), 1.996; 95% confidence interval (CI), 1.465-2.720] and DFS (P<0.001; HR, 1.824; 95% CI, 1.315-2.531). By the Kaplan-Meier method, the stage of disease and lymph node status demonstrated a significant effect on OS and DFS. Patients with the lymph node status N3 and stage III disease possessed a poor prognosis and survival. An association between lymph node status and the tumor recurrence and mortality rate was identified. The area under the curves of the lymph node status for TNBC recurrence and mortality were 0.676 (P=0.002) and 0.685 (P=0.001), respectively. Additionally, the number of pregnancies was associated with tumor size, lymph node status and stages of disease. Lymph node status is an independent prognostic indicator of OS and DFS to TNBC patients with FEC adjuvant chemotherapy.

Introduction

Breast cancer is one of the most common malignancies and leading causes of cancer-associated mortalities among females (1). Based on DNA microarray techniques, breast cancer is classified into five subtypes: Luminal A; luminal B; normal breast-like; human epidermal growth factor receptor 2 (HER2/neu) overexpressing; and basal-like (2). The subtype that is immunohistochemically characterized by the lack of expression of the estrogen receptor (ER), progesterone receptor (PR) and HER2 is defined as triple negative breast cancer (TNBC) (3).

TNBC, which accounts for 10-15% of breast cancers, is considered to exhibit an aggressive clinical behavior and poor prognosis, due to the insensitivity of the cancer to endocrine and targeted therapy (4-12). Therefore, chemotherapy is a significant therapy for such cancers. The treatment options for TNBC include anthracyclines, taxanes, platinum and alkylating agents (13-16). However, there is no standard chemotherapy regimen for TNBC.

Based on National Comprehensive Cancer Network guidelines, the adjuvant 5-fluorouracil, epirubicin and cyclophosphamide (FEC) chemotherapy regimen is the suggested regimen for breast cancer. However, there is no conclusion regarding the clinicopathological and demographical factors of TNBC patients that are suitable for adjuvant FEC chemotherapy. Therefore, the aim of the present retrospective study

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Abbreviations: TNBC, triple negative breast cancer; FEC, fluorouracil, epirubicin and cyclophosphamide; OS, overall survival; DFS, disease-free survival; AUC, area under curve; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2

Key words: triple negative breast cancer, fluorouracil, epirubicin, cyclophosphamide, overall survival, disease-free survival, lymph node status

is to analyze the association between the clinicopathological and demographical characteristics and the survival of TNBC patients that receive FEC adjuvant chemotherapy.

Materials and methods

Patients. In total, 956 patients were diagnosed with TNBC, and 25.0% (239/956) of these patients had received adjuvant FEC chemotherapy with surgery, modified radical mastectomy or breast-conserving surgery plus a sentinel lymph node examination at the Harbin Medical University (Harbin, Heilongjiang, China) between April 2001 and December 2008. These 239 patients were included in the present study. Primary cancers were evaluated in accordance with the 7th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system. The inclusion criteria included females with histologically confirmed ER, PR and HER2-negative breast cancer, between stages I and IIIA. The criteria for TNBC were 0% expression for ER, 0% expression for PR and HER2 expression of 0 or 1+ only. Patients with an immunohistochemical score for HER-2 neu of 2+ demonstrated no HER2 gene amplification by fluorescence *in situ* hybridization. These patients had not undergone neoadjuvant chemotherapy and radiotherapy prior to surgery. The exclusion criteria included stage IV disease and a history of other cancers. Pathology reports were obtained from the medical record room of the Harbin Medical University. Data on the demographical and clinical characteristics, extent of disease, and types of surgery, chemotherapy and radiotherapy were collected from the medical records. The data also included the menopausal status based on the hormone level and age, family history of cancer in first and second-degree relatives, tumor size and lymph node status. The number of pregnancies consisted of full-term pregnancies, non-full-term pregnancies and miscarriages. Clinical data of these patients were used for survival analysis.

Treatment. All patients underwent conservative surgery or a modified radical mastectomy. Chemotherapy consisting of adjuvant FEC was administered to patients (500 mg/m² cyclophosphamide, day 1; 75 mg/m² epirubicin, day 1; 500 mg/m² 5-fluorouracil, days 1 and 8, every 3 weeks, for at least 4 cycles).

Statistical Analysis. The vital status of the study group was assessed from the medical record room. January 30, 2013 was the follow-up completion date. Univariate and multivariate Cox proportional hazard models were used to assess the effects of variables on patient survival (Table I). The parameters were then tested using the multivariate Cox proportional hazards model, which was performed to identify the independent variables for predicting survival. Hazard ratios (HR) and the 95% confidence intervals (CIs) were recorded for each factor. Disease-free survival (DFS) time was calculated from the date of surgery resection to the date of the final follow-up or relapse. Overall survival (OS) time was defined as the elapsed time between the date of the surgery and the date of last follow-up or mortality. The cut-off value was selected using the receiver operating characteristic (ROC) curve analysis (Fig. 1). Survival was estimated using the Kaplan-Meier method (Fig. 2). Spearman's χ^2 test was used to analyze categorical variables

(Table II). $P < 0.05$ was considered to indicate a statistically significant difference. SPSS 19.0 software for Windows (IBM SPSS, Armonk, NY, USA) was used for statistical analysis.

Results

The demographic and clinical characteristics and the treatment options of the patients are presented in Table I. The average age of patients was 48.3 ± 9.4 years (median, 49.0 years; range, 26.0-76.0 years). The average follow-up time was 80.1 ± 30.4 months (range, 9.5-144.1 months). The number of pre-menopausal patients was 130 patients, 54.4% of the total. Of the patients, 6 (2.5%) suffered bone metastases and 25 patients (10.5%) suffered visceral metastases. The lymph node metastatic rate of patients with tumor sizes of < 2 cm was 27.9% (24/86); however, for tumor sizes of > 2 cm, the rate was as high as 48.4% (74/153).

The results of univariate analysis are shown in Table I. The univariate analysis showed that the lymph node status ($P < 0.001$) and stage of disease ($P < 0.001$) were significantly associated with the OS time. The OS time showed no significant difference for age ($P = 0.673$), menopausal status ($P = 0.574$), number of pregnancies ($P = 0.544$), family history ($P = 0.848$), tumor histology ($P = 0.717$), adjuvant radiotherapy ($P = 0.585$), primary surgery ($P = 0.607$) or tumor size ($P = 0.493$). The DFS was significantly associated with the lymph node status ($P < 0.001$) and stage of disease ($P = 0.003$), but not with the other factors. In the multivariate statistical analysis, the significant independent prognostic variable affecting survival, including OS and DFS time, was lymph node status rather than the stage of disease, despite the stage of disease being a well-characterized independent prognostic factor (Table I).

The prognostic value of lymph node status on TNBC recurrence and mortality was assessed using ROC analysis. The association of lymph node status and tumor recurrence or mortality was identified. The cut-off points for OS and DFS in the study population were each 0.5. The area under the curves (AUCs) of the lymph node status for TNBC recurrence and mortality were 0.676 ($P = 0.002$; 95% CI, 0.580-0.791) and 0.685 ($P = 0.001$; 95% CI, 0.565-0.788), respectively (Fig 1.).

The OS rates of patients following diagnosis were 97.5, 92.1 and 71.1% at 12, 36 and 60 months, respectively; the DFS rates were 95.0, 88.3 and 69.0%, respectively (Fig. 2). The Kaplan-Meier survival curves stratified for lymph node status and stage of disease are exhibited in Fig. 2. Patients with N3 or stage III disease tended to demonstrate a shorter OS and DFS compared with patients with N0-2 (OS, $P < 0.001$; DFS, $P < 0.001$) or stage I-II disease (OS, $P = 0.001$; DFS, $P = 0.005$) (Fig. 2.).

The tumor size, lymph node status and stage of disease were all associated with the number of pregnancies. Additionally, the lymph node status and stage of disease were associated with primary surgery, and the lymph node status was associated with adjuvant radiotherapy (Table II).

Discussion

The results of the present study demonstrated that age (45.6 vs. 54.4%) and menopausal status (54.4 vs. 45.6%) did not significantly affect the incidence of TNBC in China. This is

Table I. The clinicopathological and demographical factors of triple-negative breast cancer patients with adjuvant fluorouracil, epirubicin and cyclophosphamide chemotherapy.

Variables	Overall survival			Disease-free survival		
	Univariate		Multivariate	Univariate		Multivariate
	HR (95% CI)	P-value	HR (95% CI)	HR (95% CI)	P-value	HR (95% CI)
Age	0.861 (0.430-1.725)	0.673		1.308 (0.613-2.793)	0.488	
Menopausal status	1.225 (0.603-2.489)	0.574		0.836 (0.399-1.754)	0.636	
Number of pregnancies	1.246 (0.613-2.533)	0.544		2.454 (1.149-5.239)	0.020	
Family history	1.094 (0.438-2.731)	0.848		0.921 (0.350-2.423)	0.868	
Tumor histology	0.767 (0.183-3.220)	0.717		0.412 (0.056-3.034)	0.384	
Adjuvant radiotherapy	1.394 (0.422-4.601)	0.585		2.066 (0.716-5.959)	0.179	
Primary surgery	1.411 (0.380-5.244)	0.607		0.708 (0.106-4.717)	0.721	
pT stage	1.254 (0.657-2.393)	0.493		1.238 (0.626-2.450)	0.539	
pN stage	1.996 (1.465-2.720)	<0.001	1.996 (1.465-2.720)	1.824 (1.315-2.531)	<0.001	1.824 (1.315-2.531)
TNM stage	2.901 (1.640-5.132)	<0.001		2.442 (1.357-4.395)	0.003	

The variables were used due to the prognostic significance. For univariate analyses, a forward, stepwise selection (forward likelihood ratio) was used and $P<0.050$ indicated a statistically significant difference. For multivariate analyses, a Cox proportional hazards regression model was used. HR, hazard ratio; CI, confidence interval; pT, pathological assessment of primary tumor size pN, pathological assessment of regional lymph nodes; TNM, pathological assessment of anatomic stage.

Table II. Correlation between the pT, pN and TNM stages, and the clinicopathological and demographic characteristics of patients with triple-negative breast cancer patients.

Variables	Patients, n	pT classification, n			pN stage, n				TNM stage, n								
		T1	T2	T3	Correlation (P-value)		N0	N1	N2	N3	Correlation (P-value)		I	II	III	Correlation (P-value)	
All cases	239																
Age																	
<48 years	109	34	69	6													
≥48 years	130	52	74	4													
Menopausal status																	
Premenopausal	130	44	80	6													
Postmenopausal	109	42	63	4													
Number of pregnancies																	
≥2	95	26	64	5													
≤1	144	60	79	5													
Family history																	
Yes	40	15	24	1													
No	199	71	119	9													
Tumor histology																	
Ductal adenocarcinoma	219	86	133	0													
Non-ductal adenocarcinoma	20	0	10	10													
Adjuvant radiotherapy																	
Yes	19	7	12	0													
No	220	79	131	10													
Primary surgery																	
Modified radical mastectomy	227	77	140	10													
Conservative surgery	12	9	3	0													

^aP<0.05; ^bP<0.01. pT, pathological assessment of primary tumor size; pN, pathological assessment of pathological regional lymph nodes; TNM, pathological assessment of anatomic stage.

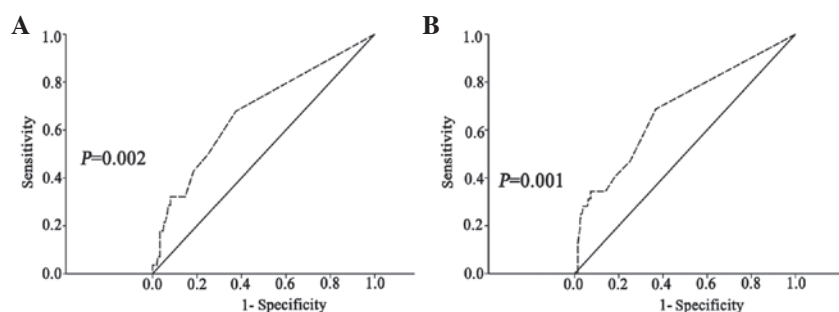


Figure 1. Receiver operating characteristic curves of the effect of lymph node status on TNBC recurrence and mortality. (A) The AUC of lymph node status for TNBC recurrence was 0.676 and $P=0.002$. (B) The AUC of lymph node status for TNBC-associated mortality was 0.685 and $P=0.001$. AUC, area under the curve; TNBC, triple-negative breast cancer.

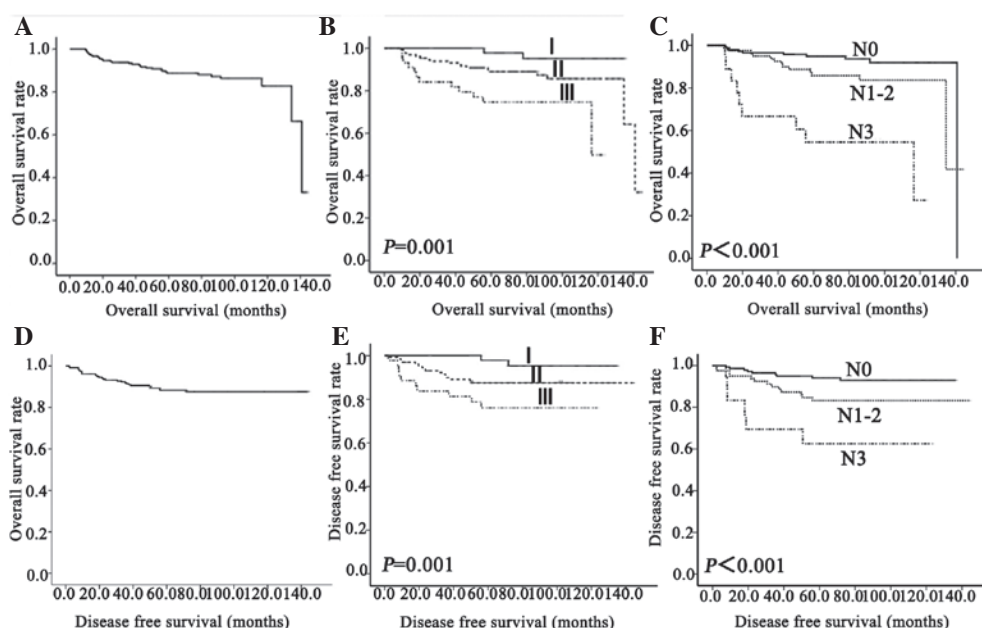


Figure 2. The effect of clinicopathological factors on the OS and DFS rates of triple negative breast cancer patients that underwent adjuvant chemotherapy with fluorouracil, epirubicin and cyclophosphamide. Prognostic significance was assessed using Kaplan-Meier survival estimates and log-rank tests. Graphs compare the OS rates according to (A) all patients, (B) the stage of disease ($P=0.001$) and (C) lymph node status ($P<0.001$). Graphs compare the DFS rates according to (D) all patients, (E) the stage of disease ($P=0.005$) and (F) lymph node status ($P<0.001$). OS, overall survival, DFS, disease-free survival.

not in accordance with the findings of previous studies, which report the prevalence of TNBC among non-African female breast cancer patients as between 10 and 17% and report that TNBC is increased in menopausal females compared with pre-menopausal African females (17-19). Numerous studies have demonstrated that premenopausal African-American females were more prone to develop TNBC (5,9,17,18). Carey *et al* reported that the morbidity rate of the TNBC subtype among African-American breast cancer patients <50 years old is as high as 39%, whereas among Caucasian females and post-menopausal African-American females, the morbidity rate is 16 and 14% respectively (5,9,18).

TNBC is prone to local recurrence and distant metastasis. In the present study, 6 patients (2.5%) suffered bone metastases and 25 patients (10.5%) suffered visceral metastases. TNBC has an increased risk of local recurrence or distant metastasis following the final diagnosis (5,17,18,20-22). In the present study, the general disease progression rate is 12.1% (29/239, the local recurrence rate is 6.7% (16/239) and the

distant metastasis rate is 8.8% (21/239). These findings suggest that distant metastasis may exhibit a certain organ tendency in TNBC (23-25) and that the specific target organ metastasis may be associated with specific gene expression (26-28). Dent *et al* observed that the frequency of distant metastasis was significantly increased among patients with TNBC compared with non-TNBC patients (33.9 and 22.4%, respectively), and the risk of distant metastasis was found to be increased in the TNBC group (relative risk = 2.6) (18). There was a gradual increase in the risk of distant metastasis in the TNBC group, with a peak in the 2nd and 3rd years (18), followed by a rapid decline, with a lower risk in the 5th year and no distant metastasis in the 8th year of follow up (29). Previous studies also reported that TNBC was associated with an increased risk of visceral metastasis and a decreased risk of bone metastasis (30,31). These results are similar to those indicated in the present study.

The variation in the tumor size was not of notable importance in patients with TNBC that possessed no distant metastasis, and had received adjuvant FEC chemotherapy.

The benefit of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy to patients with triple-negative, node-negative breast cancer is notable (32). One previous study indicated that there was no additional benefit associated with the cyclophosphamide, epirubicin and 5-fluorouracil (CEF) regimen over CMF, suggesting that non-anthracycline regimens may be sufficient in intrinsic subtypes; however, additional studies are required (33).

Therefore, the lymph node status, not stage of disease, was regarded as an independent prognostic indicator for OS and DFS. For this reason, the present study considered that the patients with large numbers of lymph node metastasis may not be suitable for FEC adjuvant chemotherapy, but may receive taxane-containing chemotherapy regimens. A previous study reported that patients with node-positive breast cancer responded better to docetaxel compared with fluorouracil (34).

In total, 40 of the 239 TNBC patients (16.7%) in the present study had a family history of breast cancer, which was not significantly increased compared with the non-TNBC subgroup total of 13% reported by Bhatti *et al* (35). Haffty *et al* concluded that TNBC exhibits an increased proportion of positive family history of breast cancer (36). Zhang *et al* reported that, in China, there was no statistically significant difference in the family history of TNBC and non-TNBC groups (37).

For tumor sizes of <2 cm, the rate of lymph node metastasis was 27.9% (24/86), compared with 48.4% for tumor sizes of >2 cm (74/153). Therefore, tumor size was not indicated to be associated with lymph node metastasis, which is in agreement with several studies (17,36,38). The present study, which assessed the association between tumor size and lymph node metastasis, produced varying results. Kandel *et al* demonstrated that 50% of patients with TNBC developed lymph node metastases when the average tumor size of TNBC was 2 cm (39). However, Haffty *et al* suggested that tumor size was not associated with lymph node metastasis (36).

Additionally, in the first year after diagnosis in the present study, the DFS rate for patients with TNBC was 95.0% (227/239), which was increased compared with that in the non-TNBC group of another study (18). This finding may be attributed to the indication that TNBC appears to be more sensitive to chemotherapy compared to non-TNBC (40). Therefore, patients with TNBC may achieve increased short-term DFS rates. In brief, TNBC patients have a poorer OS time and tend to relapse sooner compared with patients with other breast cancer subtypes (41). The present study reports that lymph node status is an effective prognostic parameter for TNBC patients, particularly for those that exhibit the N3 stage of disease; however, the effect of stages of disease is decreased. Therefore, a larger sample size is required in order to verify the results of the present study. In summary, the present study presents evidence that lymph node status may predict the prognosis of TNBC patients receiving FEC adjuvant chemotherapy in China. Patients with N0-2 may obtain the most benefit from FEC.

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