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Original Article

Prognostic value of ultrasound BI-RADS classification in triple-negative breast cancer patients received neoadjuvant chemotherapy

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Abstract: Objective: To investigate the prognostic value of ultrasound Breast Imaging-Reporting And Data System (BI-RADS) classification in patients with triple-negative breast cancer who received neoadjuvant chemotherapy. Methods: One hundred fourteen triple-negative breast cancer patients who received neoadjuvant chemotherapy in our hospital from October 2006 to December 2015 were recruited in the study. The Kaplan-Meier curve was used to analyze the patient's disease-free survival (DFS) and the overall survival (OS). Cox proportional risk model with univariate and multivariate analysis was used to evaluate the prognostic value of BI-RADS classification. Results: Of the 114 triple-negative breast cancer patients, 60 were BI-RADS 4, and 54 were BI-RADS 5. Kaplan-Meier survival analysis showed lower 5-year DFS rate and 5-year OS rate in BI-RADS 5 than in BI-RADS 4 ($P<0.05$). The results of univariate analysis showed that the BI-RADS classification was negatively correlated with 5-year DFS rate (Hazard Ratio (HR): 1.749, 95% Confidence interval (CI): 1.166-2.623, $P=0.007$), and negatively correlated with 5-year OS rate (HR: 2.102, 95% CI: 1.351-3.272, $P=0.001$). The results of multivariate analysis showed that ultrasonic BI-RADS classification was an independent predictor of DFS and OS ($P<0.05$). Conclusions: Ultrasonic BI-RADS classification may be an independent prognostic factor for triple-negative breast cancer patients receiving neoadjuvant chemotherapy. However, large scale and prospective studies are still needed for verification.

Keywords: Triple-negative breast cancer, prognosis, breast ultrasound, breast imaging-reporting and data system

Introduction

Breast cancer is the most common cancer in China and the world, and the number of patients who die from breast cancer every year is still very large [1]. Triple-negative breast cancer (TNBC) is a special subtype of breast cancer with a high recurrence rate and distant metastasis rate, resulting in the worst prognosis [2]. Neoadjuvant chemotherapy can reduce the size of cancer in patients with breast cancer, increase the chance of breast conserving treatment, and evaluate the efficacy of patients with chemotherapy drugs [3]. It is important to predict the prognosis of TNBC patients receiving neoadjuvant chemotherapy, which will affect the treatment decision of the clinician.

At present, the main prognostic factors of breast cancer include the size, classification, staging, and molecular typing of the tumor. Although some new prognostic indicators, including inflammation-related indicators, genotyping, circulating tumor cells, and tumor-infiltrating lymphocytes, have been explored [4-13]. However, it has not yet entered the clinical application, because the prognostic value of these indicators has not been determined and it is of high cost.

The breast imaging reporting and data system (BI-RADS) was founded by the American Radiology Society, aiming to standardize mammography reports and facilitate communication between radiologists and clinicians [14]. Mammography is considered to be the best screening method for breast cancer [15, 16]. Ultrasound is a complementary examination method for dense breast cancer or a high-risk group of breast cancer who cannot perform magnetic resonance imaging for some reason. At present, the ultrasonic BI-RADS classifica-

Table 1. Patient characteristics

	Number of patients
BI-RADS classification	
4	60
5	54
Age (years)	
≤50	81
>50	33
Tumor grade	
Grade 1	9
Grade 2	70
Grade 3	33
Unknown	2
T stage	
T1	29
T2	68
T3	15
T4	2
N stage	
N0	62
N1	34
N2	5
N3	13
AJCC stage	
I	20
II	72
III	22

tion has good reliability and effectiveness in the diagnosis of breast tumors [15]. However, there are few studies on the prognostic value of ultrasound BI-RADS classification for breast cancer patients. The aim of this study was to explore the prognostic value of BI-RADS classification in triple-negative breast cancer patients who received neoadjuvant chemotherapy.

Materials and methods

Patients

In this study, 114 triple-negative breast cancer patients who received neoadjuvant chemotherapy at The Third Affiliated Hospital of Soochow University from October 2006 to December 2015 were recruited. Less than 10% of the expression of estrogen receptor (ER) and progesterone receptor (PR) was identified as negative. Human epidermal growth factor receptor-2 (Her-2) negative was determined by immunohistochemistry or fluorescence *in situ* hybridization (FISH). All the patients were diagnosed as triple-negative breast cancer by pathology, and the breast ultrasound examination was performed before the neoadjuvant chemotherapy and the BI-RADS classification was evaluated. We excluded metastatic breast cancer, inflammatory breast cancer, and patients with other tumors. This study was approved by the Ethical Committee of The Third Affiliated Hospital of Soochow University.

Table 2. Correlation between BI-RADS and clinicopathologic parameters

Parameter	BI-RADS		
	4	5	P
Age (years)			
≤50	41	40	0.500
>50	19	14	
Tumor grade			
Grade 1	5	4	0.606
Grade 2	39	31	
Grade 3	15	18	
T stage			
T1	20	9	0.196
T2	32	36	
T3	7	8	
T4	1	1	
N stage			
N0	36	26	0.468
N1	14	20	
N2	3	2	
N3	7	6	
AJCC stage			
I	14	6	0.197
II	34	38	
III	12	10	

Clinicopathological information and treatment

Clinicopathological information was collected from hospital's electronic medical record management system, including age, tumor classification, tumor size, lymph node staging, and tumor staging (American Cancer Commission [AJCC]-7 criteria). All patients received neoadjuvant chemotherapy and surgical treatment.

Ultrasonic BI-RADS classification

According to the fifth edition of the BI-RADS classification: BI-RADS 1 is negative; BI-RADS 2 is a benign tumor; BI-RADS 3 is considered a benign tumor and recommends re-examination after 6 months; BI-RADS 4 is suspected

Table 3. Correlation between clinicopathologic parameters and 5-year DFS

Parameter	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
BI-RADS				
4	1		1	
5	1.749 (1.166-2.623)	0.007	1.609 (1.066-2.43)	0.024
Age (years)				
≤50	1		1	
>50	1.003 (0.983-1.023)	0.797	1.013 (0.99-1.036)	0.281
Tumor grade				
Grade 1-2	1		1	
Grade 3	2.269 (1.446-3.561)	<0.001	1.964 (1.234-3.127)	0.004
T stage				
T1	1		1	
T2-4	1.964 (1.24-3.11)	0.004	1.962 (0.885-4.348)	0.097
N stage				
N0	1		1	
N1-3	1.337 (0.902-1.981)	0.149	1.237 (0.776-1.971)	0.372
AJCC stage				
I	1		1	
II-III	1.838 (1.086-3.111)	0.023	0.942 (0.351-2.528)	0.905

malignancy and suggested biopsy; BI-RADS 5 is highly suggestive of malignancy and suggests biopsy; BI-RADS 6 is a confirmed malignant tumor.

Follow-up

The deadline for follow-up of this study was August 12, 2017. Primary endpoints were disease-free survival (DFS) and total survival (OS). DFS was defined as the time from the diagnosis to the occurrence of disease recurrence, metastasis, death, or the end of the follow-up. OS was defined as the time from the diagnosis to the death or the end of the follow-up.

Statistical analysis

Chi-square test was used to evaluate the relationship between the BI-RADS classification and the patient's clinicopathological features. Kaplan-Meier and log-rank tests are used to analyze patients' DFS and OS. Cox proportional risk model with univariate and multivariate analysis was used to evaluate the risk ratio (HR) and its 95% confidence interval (95% CI). $P<0.05$ was considered statistically significant. Statistical analyses of data were conducted using SPSS 21 (IBM Corporation, Armonk, NY, USA).

Results

Clinicopathological information

In this study, 114 patients with triple-negative breast cancer receiving neoadjuvant chemotherapy were recruited. **Table 1** summarizes the clinicopathological information of all patients. Of these, 60 patients were BI-RADS 4, and 54 were BI-RADS 5. There were 81 cases of age less than 50 years old, 33 cases more than 50 years old; 9 cases of tumor grade 1, 70 cases in grade 2, 33 in class 3 and 2 with unknown classification; there were 29 cases of T1, 68 cases of T2, 15 cases of T3, and 2 cases of T4 in breast cancer patients; for lymph node classification, there were 62 cases of N0, 34 cases of N1, 5 cases of N2, and 13 cases of N3; The patients with AJCC stage for 1-III stage were 20, 72 and 22, respectively. At the end of the follow-up, 84 patients reached the end of the study. Seven cases were lost to follow up.

The relationship between BI-RADS and clinicopathological parameters

Table 2 summarizes the relationship between the BI-RADS classification and the clinicopathological features of the patients. The results showed that the T staging of patients may be positively correlated with the BI-RADS classification, but did not reach statistical difference ($P=0.196$); the AJCC classification may be positively correlated with the BI-RADS classification, but did not reach statistical difference ($P=0.197$). The patient's age, tumor grading, and lymph node classification were not found had obvious correlation with the BI-RADS classification.

The relationship between BI-RADS and 5-year DFS rate

Table 3 summarizes the relationship between the BI-RADS classification as well as other clinicopathological information and the patient's

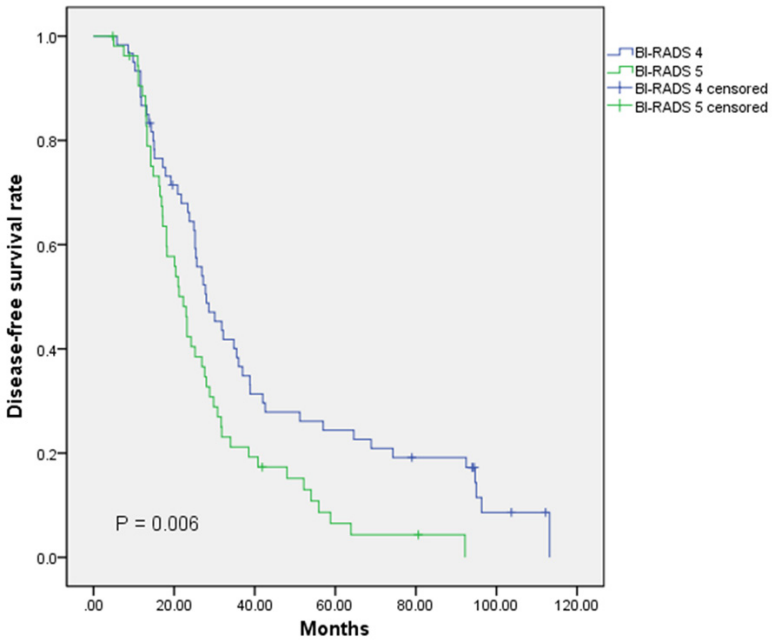

Figure 1. Disease-free survival rate of triple-negative breast cancer patients according to BI-RADS.

Table 4. Correlation between clinicopathologic parameters and 5-year OS

Parameter	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
BI-RADS				
4	1		1	
5	2.102 (1.351-3.272)	0.001	2.088 (1.309-3.329)	0.002
Age (years)				
≤50	1		1	
>50	1.007 (0.983-1.031)	0.594	1.011 (0.985-1.037)	0.427
Tumor grade				
Grade 1-2	1		1	
Grade 3	2.867 (1.77-4.642)	<0.001	2.546 (1.552-4.176)	<0.001
T stage				
T1	1		1	
T2-4	1.954 (1.153-3.312)	0.013	1.958 (0.834-4.598)	0.123
N stage				
N0	1		1	
N1-3	1.481 (0.962-2.28)	0.074	1.335 (0.801-2.223)	0.268
AJCC stage				
I	1		1	
II-III	1.804 (0.975-3.337)	0.060	0.721 (0.248-2.098)	0.549

DFS. The results of survival analysis show that the 5-year DFS rate in BI-RADS 5 is worse than in BI-RADS 4 (**Figure 1**). The results of univariate analysis show that the BIRADS classification is negatively correlated with 5-year DFS rate (HR: 1.749, 95% CI: 1.166-2.623, P=0.007, **Table 3**); tumor grade, T stage, AJCC stage were also negatively related with 5-year DFS rate (P<0.05). The results of multivariate analysis show that BI-RADS classification is an independent predictor of 5-year DFS rate (HR: 1.609, 95% CI: 1.066-2.43, P=0.024); tumor grade is also an independent predictor of 5-year DFS rate (P=0.004).

The relationship between BI-RADS and 5-year OS rate

Table 4 summarizes the relationship between BI-RADS classification and the clinicopathological information and the patient's OS. The results of survival analysis show that the 5-year OS rate in BI-RADS 5 was worse than in BI-RADS 4 (**Figure 2**). The results of univariate analysis show that the BI-RADS classification is negatively correlated with 5-year OS rate (HR: 2.102, 95% CI: 1.351-3.272, P=0.001, **Table 4**); Tumor grade, N stage was also negatively related to 5-year OS rate (P<0.05). The results of multivariate analysis show that BI-RADS classification is an independent predictor of 5-year OS rate (HR: 2.088, 95% CI: 1.309-3.329, P=0.002); tumor grade is also an independent predictor of 5-year OS rate (P<0.004).

Discussion

This study found that ultrasound BI-RADS classification is negatively correlated with DFS and OS in triple-negative breast cancer patients receiving neoadjuvant chemotherapy. The results of multivariate analysis showed that ultrasonic BI-RADS classification is an independent predictor of DFS and OS in patients.

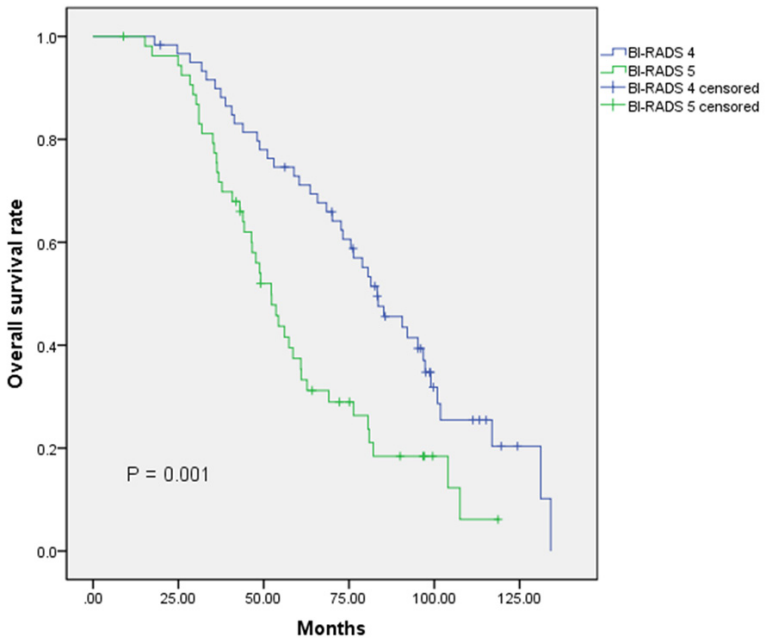

Figure 2. Overall survival rate of triple-negative breast cancer patients according to BI-RADS.

At present, the study of breast BI-RADS classification mostly focuses on predicting malignant diseases or finding other diseases that need surgical treatment [16-18]. However, few studies have explored the relationship between BI-RADS classification and tumor characteristics and patient survival. Irshad et al. [19] suggest that the presence of post-ultrasonic shadow is closely related to ER-positive and low-grade tumors. However, posterior enhancement is associated with ER negative and high-grade tumors. Our study found that the size of the tumor may be positively correlated with the classification of BI-RADS. The correlation analysis between the AJCC classification and the BI-RADS classification did not reach statistical difference, but it still suggested a correlation between the two.

Two studies were conducted to analyze the correlation between breast ultrasound BI-RADS classification and the prognosis of breast cancer patients. Kuo et al. [20] found that patients with class BI-RADS 5 had a higher risk of recurrence and poorer survival than those of the BI-RADS 0-4. Kim et al. [21] found that in breast cancer patients, DFS is worse in BI-RADS 5 patients than in BI-RADS 4 patients. Subgroup analysis showed that in I stage breast cancer, BI-RADS 5 was a bad prognostic factor for DFS in breast cancer patients. However, these above studies have not explored the prognostic value of BI-RADS classification in the various molecular subtypes of breast cancer. The results of our study show that BI-RADS classification is negatively correlated with DFS and OS in triple-negative breast cancer patients receiving neoadjuvant chemotherapy. We found that ultrasonic BI-RADS classification is an independent predictor of DFS and OS in multivariate analysis that enrolled clinicopathological features associated with the prognosis of breast cancer patients.

There are some limitations in this study. First, the sample size is small. Second, since this is a retrospective study, there may be a selection bias. Third, the BI-RADS classification is only evaluated by a radiologist and may have errors. Nevertheless, the results of this study suggest that ultrasonic BI-RADS classification is an independent predictor of DFS and OS for triple-negative breast cancer patients receiving neoadjuvant chemotherapy.

Conclusions

The results of this study suggest that ultrasonic BI-RADS classification may be an independent prognostic factor for triple-negative breast cancer patients receiving neoadjuvant chemotherapy. However, large scale and prospective studies are still needed for verification.

Disclosure of conflict of interest

None.

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