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Original Article

Prognostic roles of ultrasound-based BI-RADS classification in Her2+ breast cancer patients

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Abstract: The aim of the current study was to explore the prognostic significance of ultrasound-based Breast Imaging-Reporting and Data System (BI-RADS) classification in patients with human epidermal growth factor receptor-2 positive (Her2+) breast cancer. A total of 344 Her2+ breast cancer patients, treated from April 2005 to January 2016, were recruited. Overall survival (OS) and disease-free survival (DFS) were evaluated using Kaplan-Meier curves. The prognostic value of BI-RADS classification was evaluated using Cox's proportional risk model, along with univariate and multivariate analyses. Results showed that the 344 Her2+ breast cancer patients consisted of 190 BI-RADS 5 patients, 152 BI-RADS 4 patients, and 2 BI-RADS 3 patients. OS and DFS scores of patients with BI-RADS 3-4 were better than those with BI-RADS 5 ($P < 0.001$, $P = 0.005$), according to Kaplan-Meier survival analysis. Univariate analysis yielded a negative correlation between BI-RADS classification and OS in Her2+ breast cancer patients (Hazard Ratio (HR): 2.146, 95% Confidence interval (CI): 1.481-3.111, $P < 0.001$) and between BI-RADS classification and DFS (HR: 1.591, 95% CI: 1.147-2.208, $P = 0.005$). Multivariate analysis, in contrast, established ultrasonic BI-RADS classification as an independent predictor of OS and DFS in Her2+ breast cancer patients ($P < 0.05$). In conclusion, increased classification of ultrasound-based BI-RADS classification levels is a risk factor for poor survival in patients with Her2+ breast cancer.

Keywords: Her2, breast cancer, prognosis, breast imaging-reporting and data system

Introduction

In China, breast cancer is the most common cancer type in women. Numerous patients die of the disease every year [1-3]. Overexpression of human epidermal growth factor receptor-2 (Her2) is an adverse prognostic factor in breast cancer. Her2 positive breast cancer (that is, Her2 overexpression, with ER and PR not expressed) has the potential for high malignancy, easy recurrence, and distant metastasis [4-6]. Targeted drugs (such as Herceptin) for Her2-overexpressed patients have been widely used in clinical practice. Although survival times and quality of life scores of breast cancer patients have been significantly improved using these drugs, there are still many deaths each year [4, 5].

The breast imaging reporting and data system (BI-RADS) was founded by the American Radiology Society. The purpose of the system is to standardize mammography reports, making communication between radiologists and clinicians more convenient [7]. To date, the best screening method for breast cancer is mammography. Ultrasound-based BI-RADS classification has good reliability and effectiveness in the diagnosis of breast tumors [8, 9]. However, few studies have investigated the prognostic roles of ultrasound-based BI-RADS classification in breast cancer patients [10, 11]. Main prognostic parameters for Her2+ breast cancer include tumor size, staging, and differentiation. Some new prognostic indicators, such as tumor infiltrating lymphocytes, circulating tumor cells, and inflammation-related indicators, have also been explored [12-35]. However, the prognostic value of these indicators has not been confirmed and costs are high. Therefore, they have not been used in clinical tests. The purpose of this research was to explore the prognostic value of ultrasound-based BI-RADS classification in patients with Her2+ breast cancer.

Table 1. Clinicopathologic parameters of 344 Her2+ breast cancer patients

Parameters	Number of patients
Age (years)	
≤ 50	242
> 50	102
T stage	
T1	68
T2	192
T3	72
T4	12
N stage	
N0	140
N1	72
N2	52
N3	80
AJCC stage	
I	52
II	150
III	142
Tumor grade	
Grade 1	46
Grade 2	172
Grade 3	106
Unknown	20
Type of surgery	
Breast-conserving surgery	36
Radical mastectomy	308
BI-RADS classification	
3	2
4	152
5	190

Materials and methods

Subjects

This study was approved by the Ethics Committee of Qingdao Chengyang People's Hospital. A total of 344 cases of Her2+ breast cancer, diagnosed and treated from April 2005 to January 2016, were enrolled in this study. Breast tumor tissues were obtained by surgery and tested for expression of Her-2, ER, and PR. Immunohistochemistry or fluorescence *in situ* hybridization (FISH) were used to determine Her-2 positivity. Expression values for ER and PR < 10% were identified as negative. All patients included in the study were diagnosed with Her2+ breast cancer, according to pathology. Breast ultrasound testing was completed and BI-RADS classification was evaluated before anti-cancer treatment. Patients with inflammatory breast cancer, metastatic breast cancer, and other tumors were excluded from the study.

An electronic medical record management system was used to collect clinical and pathological information of patients, including age, tumor differentiation, tumor size, lymph node staging, and tumor stage (American Cancer Commission [AJCC]-7 criteria). All breast cancer patients were treated with surgery and postoperative adjuvant chemoradiotherapy or neoadjuvant chemotherapy and surgery.

Follow-ups were regularly preformed every 3 months after surgery for all patients. The deadline for follow-ups was August 12, 2018. Primary endpoints were disease-free survival (DFS) and overall survival (OS), with DFS defined as the time from diagnosis to disease recurrence, metastasis, death, or the end of follow-up. OS is defined as the time from diagnosis to death or the end of follow-up.

BI-RADS classification

According to the fifth edition of BI-RADS classification, BI-RADS 6 is confirmative of a malignant tumor. BI-RADS 5 is highly suggestive of malignancy and proposes biopsy. BI-RADS 4 represents suspected malignancy and suggests biopsy. BI-RADS 3 is considered representative of benign tumors and recommends reexamination after 6 months. BI-RADS 2 is indicative of a benign tumor and BI-RADS 1 indicates a negative status.

Statistical analysis

Kaplan-Meier and log-rank tests were used to analyze patient DFS and OS, while Chi-squared tests were used to evaluate relationships between BI-RADS classification and patient clinicopathological features. Risk ratios (HR) and its 95% confidence intervals (95% CI) were assessed using Cox's proportional risk model, along with univariate and multivariate analyses. $P < 0.05$ indicates statistical significance. Data analysis was performed using SPSS 21 (IBM Corporation, Armonk, NY, USA).

Results

Clinical and pathological information

A total of 344 patients with Her2+ breast cancer were recruited for this study. **Table 1** summarizes the clinicopathological information of all patients. Of the 344 patients, 190 were

Table 2. Association between clinicopathologic parameters and BI-RADS classification

Parameter	BI-RADS		*P* value
	3-4	5	
Age (years)			
≤ 50	108	134	0.936
> 50	46	56	
T stage			
T1	46	22	< 0.001
T2-4	108	168	
N stage			
N0	78	62	0.001
N1-3	76	128	
AJCC stage			
I	38	14	< 0.001
II-III	116	176	
Tumor grade			
Grade 1-2	110	108	0.031
Grade 3	40	66	

BI-RADS 5 cases, 152 were BI-RADS 4, and 2 were BI-RADS 3. A total of 102 patients were less than 50 years old, while 242 patients were more than 50 years old. Moreover, 36 patients underwent breast-conserving surgery, while 308 patients received a radical mastectomy. There were 68 cases of tumor size T1, 192 cases of T2, 72 of T3, and 12 of T4. There were 46 cases of tumor grade 1, 172 cases of grade 2, 106 of grade 3, and 20 with unknown classification. For lymph nodes, there were 140 cases of N0, 72 cases of N1, 52 cases of N2, and 80 cases of N3. There were 52, 150, and 142 cases, respectively, under AJCC stages I-III classification. A total of 244 patients completed the study up to the end of follow-up. Unfortunately, 22 patients were lost follow-up.

Correlation between BI-RADS and clinicopathological characteristics

Relationships between BI-RADS classification and clinicopathological features are summarized in **Table 2**. Patients with high T stage, N stage, AJCC stage, and tumor grades had higher proportions of BI-RADS 5 than those with low T stage, N stage, AJCC stage, and tumor grades (all P < 0.05).

Prognostic value of BI-RADS concerning OS of Her2+ breast cancer patients

Relationships between BI-RADS classification/clinicopathological information and OS of patients with Her2+ breast cancer are summarized in **Table 3**. Survival analysis showed that the median OS of BI-RADS 3-4 patients was better than that of BI-RADS 5 patients (95.5 *vs* 68.4 months, P < 0.001, **Figure 1**). According to univariate analysis, BI-RADS classification correlated negatively with OS (HR: 2.146, 95% CI: 1.481-3.111, P < 0.001, **Table 3**). T stage, tumor grade, N stage, and AJCC stage also correlated negatively with OS (P < 0.001). Multivariate analysis revealed BI-RADS classification as an independent predictor of OS in Her2+ breast cancer patients (HR: 1.596, 95% CI: 1.126-2.262, P = 0.003). T stage, tumor grade, N stage, and AJCC stage were also identified as independent OS predictive factors (P < 0.05).

Prognostic value of BI-RADS concerning DFS of Her2+ breast cancer patients

Relationships between BI-RADS classification/clinicopathological information and DFS of Her2+ breast cancer patients are summarized in **Table 4**. Survival analysis showed that the median DFS of BI-RADS 3-4 patients was better than that of BI-RADS 5 patients (39.0 *vs* 29.6 months, P = 0.005, **Figure 2**). According to univariate analysis, BI-RADS classification correlated negatively with DFS (HR: 1.591, 95% CI: 1.147-2.208, P=0.005, **Table 4**). T stage, tumor grade, N stage, and AJCC grade also correlated negatively with DFS (P < 0.05). Multivariate analysis revealed BI-RADS classification as an independent predictor of DFS (HR: 1.415, 95% CI: 1.003-1.995, P = 0.048). T stage, tumor grade, N stage, and AJCC grade were also identified as independent predictors of DFS (P < 0.05).

Discussion

The current study revealed that ultrasound BI-RADS classification is negatively related to OS and DFS levels of patients with Her2+ breast cancer. According to results from multivariate analysis, ultrasonic BI-RADS classification was an independent predictor of OS and DFS in breast cancer patients. In addition, T staging, N staging, and AJCC staging were found to be correlated positively with BI-RADS classification.

Previous studies have analyzed the correlation between breast ultrasound BI-RADS classification and prognosis of breast cancer patients.

Table 3. Association between clinicopathologic parameters and OS

Parameter	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)				
≤ 50	1		-	-
> 50	0.991 (0.973-1.01)	0.365	-	-
T stage				
T1	1		1	
T2-4	3.586 (2.078-6.187)	< 0.001	2.842 (1.015-4.961)	0.047
Tumor grade				
Grade 1-2	1		1	
Grade 3	3.086 (2.088-4.561)	< 0.001	2.014 (1.315-3.085)	0.001
N stage				
NO	1		1	
N1-3	2.509 (1.714-3.673)	< 0.001	1.61 (1.005-2.581)	0.048
AJCC stage				
I	1		1	
II-III	3.765 (2.044-6.937)	< 0.001	2.752 (1.221-4.558)	< 0.001
BI-RADS classification				
3-4	1		1	
5	2.146 (1.481-3.111)	< 0.001	1.596 (1.126-2.262)	0.003

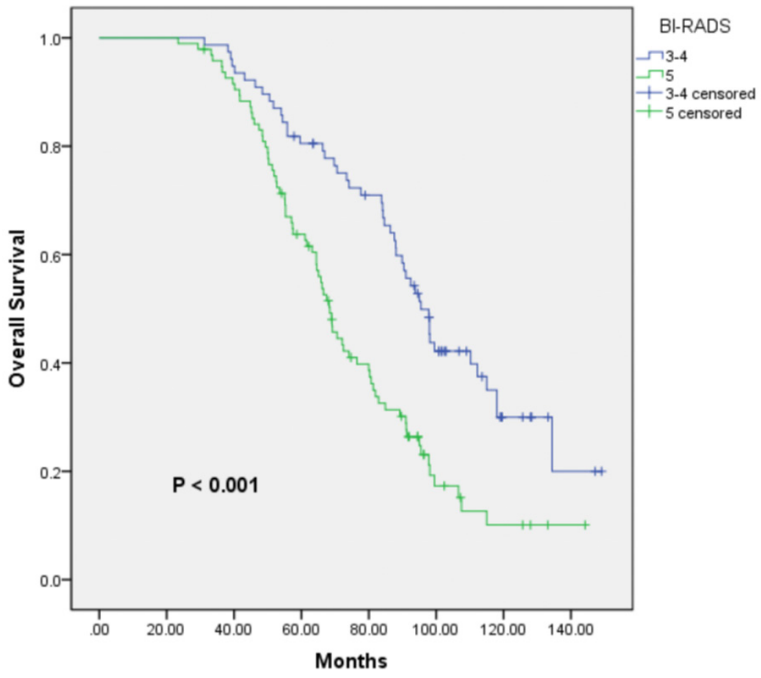

Figure 1. Overall survival of Her-2+ breast cancer patients according to BI-RADS classification.

Kim et al. reported that DFS in breast cancer patients with BI-RADS 5 was worse than that in patients with BI-RADS 3-4. Results of subgroup analysis revealed BI-RADS 5 as a bad prognostic factor for DFS in stage I breast cancer patients. Kuo et al. [10] found that patients with BI-RADS 5 had a higher risk of recurrence and poorer survival than patients with BI-RADS 0-4. The current study did not explore the prognostic value of BI-RADS classification in subtypes of breast cancer molecules. However, this study showed that BI-RADS classification correlated negatively with OS and DFS in patients with Her2+ breast cancer. Multifactor analysis found clinicopathological features to be associated with prognosis of breast cancer patients, establishing ultrasonic BI-RADS classification as an independent predictor of OS and DFS in patients.

Other studies of breast cancer-related BI-RADS classifications have mainly focused on predicting malignant diseases or finding other diseases that need surgical treatment [9, 36-38]. There is, therefore, little research concerning the relationship between BI-RADS classifications and

Table 4. Association between clinicopathologic parameters and DFS

Parameter	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)				
≤ 50	1		-	-
> 50	0.988 (0.97-1.006)	0.179	-	-
T stage				
T1	1		1	
T2-4	2.859 (1.818-4.494)	< 0.001	2.34 (1.327-3.793)	0.001
Tumor grade				
Grade 1-2	1		1	
Grade 3	3.636 (2.503-5.284)	< 0.001	2.827 (1.842-4.339)	< 0.001
N stage				
NO	1		1	
N1-3	2.327 (1.659-3.265)	< 0.001	1.619 (1.038-2.527)	0.034
AJCC stage				
I	1		1	
II-III	2.398 (1.474-3.902)	< 0.001	1.826 (1.236-3.125)	0.027
BI-RADS classification				
3-4	1		1	
5	1.591 (1.147-2.208)	0.005	1.415 (1.003-1.995)	0.048

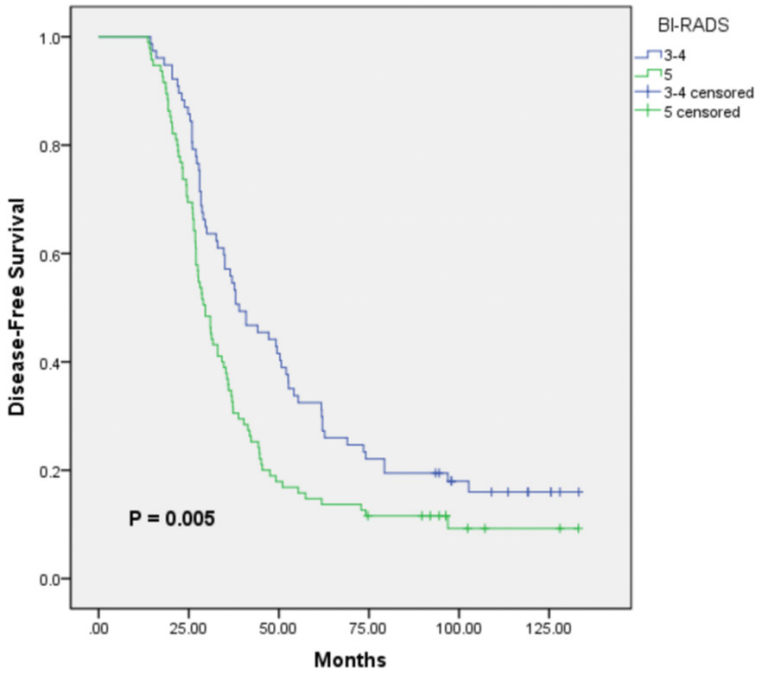

Figure 2. Disease-free survival of Her-2+ breast cancer patients according to BI-RADS classification.

patient characteristics. Irshad et al. [39] suggested that the presence of a shadow after an ultrasound is closely related to ER+ and low-grade tumors, while posterior enhancement is closely related to ER- and high-grade tumors. The current study backs this claim, with T staging, N staging, and AJCC staging correlating positively with BI-RADS classification. Tumor classification correlated positively with BI-RADS classification, in accord with previous studies [40, 41].

To date, the current study is the largest study evaluating the prognostic roles of ultrasound-based BI-RADS classification in Her2+ breast cancer. Despite promising findings, there were several limitations to the current study. First, selection bias may exist, as this was a retrospective study. Second, errors in BI-RADS classification may exist. It was evaluated by one radiologist alone. However, results suggest that ultrasound BIRADS classification is an independent predictor of OS and DFS in patients with

Her2+ breast cancer. These results are encouraging and lay the groundwork for further in-depth evaluations.

Conclusion

The current study revealed that ultrasound-based BI-RADS classification may be a high-risk factor for poor survival in Her2+ breast cancer patients. Future in-depth investigations should shed more light on present findings.

Disclosure of conflict of interest

None.

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