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The value of ultrasound in predicting axillary node involvement in patients with early breast cancer

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Abstract

Introduction: The aim of this study was to investigate the true extent of axillary lymph nodes (ALNs), clinicopathological features and prognosis of patients with false negative axillary lymph nodes by preoperative axillary ultrasound (AUS).

Methods: This study retrospectively analyzed 3,363 primary invasive breast cancer patients who had undergone routine preoperative ultrasound (US) and surgery from January 2010 to December 2012. Finally, the follow-up data for disease-free survival (DFS) and overall survival (OS) were obtained from 1, 732 patients with a negative preoperative AUS (median follow-up of 58 months). Cox regression analysis was used to correlate biomarkers and tumor characteristics with DFS and OS.

Discussion: According to the Z0011 trial, more extensive surgery of the axilla does not provide an additional survival benefit or change the prognosis for early breast cancer patients. Recent publications suggested that early disease patients with clinically and radiologically negative axillae do not require SLNB. Thus, AUS is currently under the spotlight for its potential to reduce the need for SLNB. However, as the false-negative rates of AUS (21%-48%) are not optimal, the demand for axillary surgery remains even if AUS is negative. Our study found that in the low-risk group (patients with older age, smaller primary tumor, lower expression of Ki-67 and lower histological grade), the proportion of patients with >3 axillary lymph nodes metastasis confirmed by postoperative pathology was extremely low (1.8% - 5.3%), and there was no significant difference in the 5-year DFS and OS between the false negative and true negative group.

Conclusions: Breast cancer patients with advanced age, small tumor size, low expression of Ki-67 and low histological grade were at low risk of poor prognosis. Therefore, AUS has the potential to replace ALN surgery in these patients.

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Introduction

In recent years, the incidence rate of breast cancer is increasing obviously, and it has become one of the leading causes of death for female cancer patients [1]. ALNM is the earliest and most common metastatic pathways of breast cancer, and axillary lymph node status is one of the most important prognostic factors in breast cancer [2]. In the 1990s, the advent of sentinel lymph node biopsy (SLNB) made it possible for some patients to avoid axillary lymph node dissection (ALND) [3]. SLNB is the standard of care for staging of the axilla in patients with clinical T1-T2, N0 breast cancer currently. However, SLNB still carries morbidities, such as seroma, lymphedema, and long- term paresthesia [4,5]. Now, some researchers suggest that early disease patients with clinically and radiologically negative axillae do not require SLNB [4]. As the theory of molecular typing based on the characteristics of breast cancer gene expression and tumor morphology is accepted by most people [6,7], and predictors of tumor biology are increasingly used to make adjuvant therapy decisions, it can be seen that axillary surgery has become more and more conservative, and non-invasive has become a trend of axillary management.

AUS is one of the best non-invasive methods for evaluating ALNs. Considering cost and effect, AUS is superior to mammography and magnetic resonance imaging among patients with clinically node-negative breast cancer [8]. Aubriana M. McEvoy et al. [9] demonstrated that considering both cost and effectiveness, observation was superior to SLNB in postmenopausal women with cT1-T2 N0, HR+/HER2- breast cancer and a negative AUS. ACOSOG Z0011 randomized breast cancer patients with positive SLNB to no further axillary surgery or to completion ALND and demonstrated no overall survival advantage with ALND [10]. Since SLNB itself may represent surgical over-treatment in patients with a negative axillary ultrasound, some clinicians are interested in omitting SLNB. They believe that AUS has the potential to replace SLNB in patients with clinical T1–T2, N0 breast cancer [11]. However, several previous studies showed that preoperative AUS had the sensitivity of 50-70% and specificity of 87-95%. In addition, as the false negative rates of AUS (21%-48%) are not optimal, the demand for axillary surgery remains even if AUS is negative [12,13]. A false negative AUS may lead to understating and undertreatment. In terms of current data, AUS has been unable to replace SLNB completely [14].

Despite this, the role of AUS in axillary staging and alternatives to SLNB should be considered. Therefore, this study aims to analyze the true extent of axillary nodes and the prognosis of patients with a negative preoperative AUS. The other aim of this study is to determine which patients would benefit most from AUS evaluation for metastatic disease. We present the following article in accordance with the CONSORT reporting checklist.

Materials and methods

Patients

This retrospective study was approved by the institutional review board, and a waiver of informed consent was granted on the basis of the retrospective nature of the study and minimal risk to patients. 3,363 patients who were diagnosed as invasive breast cancer at the Breast Center of the Fourth Hospital of Hebei Medical University from January 2010 to December 2012 were selected. All patients undergoing appropriate adjuvant therapy were prescribed treatment according to national guidelines. The study was approved by the Scientific and the Ethics Committees of Fourth Hospital of Hebei Medical University (2021KY056).

All patients underwent US examination before surgery. The inclusion criteria were women who (I) had undergone mastectomy or breast conserving surgery; (II) had undergone ALND or SLNB; (III) had no severe concomitant diseases; (IV) had I - III stage invasive breast carcinoma; and (V) had complete immunohistochemistry data including estrogen receptor (ER), progesterone (PR), and human epidermal growth factor receptor 2 (HER-2). Male patients, patients who were diagnosed with bilateral tumors or distant metastases at the preoperative workup, patients with pure ductal carcinoma in situ (DCIS) and/or lobular carcinoma in situ (LCIS) and patients who received neoadjuvant chemotherapy were excluded. At last, a total of 2, 357 patients entered the final analysis.

Ultrasound images

US examinations were performed by trained radiology technicians and radiologists using Philips iu22 US system with L12-5 linear array probe and frequency 5-12 MHz conventionally. The tumor size, tumor blood flow classification, the number, length, boundaries of the cortex and medulla, and the blood flow of ALNs were documented. Multiple ALNs, invisible nodal structure, thickening of the cortex, unclear delineation of the cortex and medulla, rich blood flow signals within the lymph nodes, and aspect ratio ≥2 are defined as signs of suspicious ALNM. Lymph nodes that met one or more of its malignant signs were recorded as a positive AUS, and lymph nodes that did not meet any of those above signs of malignancy were recorded as a negative AUS.

Clinical and pathological data

ER, PR, HER-2 and Ki-67 are the routine pathological examination indexes of our hospital. According to the current diagnostic criteria, all immunohistochemistry slides for ER, PR, and HER-2 were reviewed again by two independent pathologists. Molecular typing refers to the 2015 St Gallen Consensus, which divides molecular typing into the following four groups: Luminal A, Luminal B, HER-2 enriched, and triple negative.

Follow-up

The starting point of follow-up was the day of surgery, and the end point was July 2016 or a fatal event occurred. Endpoint events were defined as deaths due to recurrence or metastasis events, or for any reason. DFS was calculated from the date of operation to the first observed recurrence (local or distant), and patients without recurrence were censored at the time of last follow-up or death. OS was defined as the time span from surgical treatment to death for various reasons. Other endpoint events or survival outcomes were classified as censored.

Statistical analysis

Statistical software was analyzed by SPSS 24.0 software, and $P<0.05$ was set as statistically different. Patients were divided into true negative group and false negative group based on ultrasound and pathological results. The clinicopathological char-

acteristics were compared using the chi-square test and binary logistic regression analysis. Survival curves were constructed with the Kaplan-Meier method, and survival rate was compared using Log-rank test. The diagnostic indices included sensitivity, specificity and negative predictive value (NPV).

Results

Clinicopathologic characteristics

A total of 3,363 breast cancer patients were eligible for enrolment during the study period. After exclusions, 2,357 patients were included in the final analysis. 1,732 patients were diagnosed as negative and 625 patients were diagnosed as positive by preoperative AUS. Of the 1,732 AUS negative patients, 405 (23.4%) were false negative and 1,327 (76.6%) were true negative (Figure 1). The sensitivity, specificity and NPV of preoperative ultrasonography in the diagnosis of ALNM were 50.55%, 85.72% and 76.62%, respectively. The most sensitive parameter of ultrasound in axillary nodes was the abnormal of lymphatic hilum (blurred or disappeared, etc.) and accuracy was 72.31%. The clinical and pathological characteristics of patients were compared between the ALNs false negative group and true negative group. Patients with false negative axillary US results were more likely to have younger age, larger primary tumor size, ER positive, PR high expression, Ki-67 high expression, and higher histological grade (Table 1).

Survival analysis of patients with a false negative AUS

The follow-up time was 42-80 months, and the median follow-up time was 58 months. Univariate analysis using the Kaplan-Meier method showed that the patients who is in false negative group with < 50 years old had a worse OS and DFS than those in true negative group. While in ≥50 years old group, there was no significant statistical difference in OS (p = 0.608) and DFS (p = 0.153) between the false negative and true negative group (Figure 2A, 2B) (Tables 2,3). Furthermore, in the primary tumor ≤2 cm (p= 0.050, p = 0.135), Ki-67≤14% (p = 0.144, p = 0.648) and the low histologic grade group (p = 0.696, p = 0.728), there was no significant difference in OS and DFS between the false negative and true negative group (Figures 2C-2H) (Tables 2,3). In addition, in the ≥50 years old, tumor ≤2 cm, Ki-67≤14%, and the low histologic grade groups, patients with >3 lymph nodes metastases accounted for only 4.4%, 5.3%, 2.2% and 4.6%, respectively. However, the expression of ER, PR, HER-2 was associated with the survival of breast cancer patients. The OS and/or DFS was significantly different between the false negative and true negative group. Therefore, this means that more extensive surgery of the axilla did not provide an additional survival benefit or change the prognosis in some part of breast cancer patients.

Table 1: Clinicopathological characteristics of false-negative and true-negative US patients.

	False negative (n=405)	True negative (n=1,327)	
Characteristic	N%	N%	*P*
Age			0.002
<50 y	237 (58.5)	662 (50.0)	
≥50 y	168 (41.5)	665 (50.0)	
Tumor size			0.003
≤2 cm	206 (50.9)	736 (55.5)	
>2 cm	164 (40.5)	425 (32.0)	
Uncertain	35 (8.6)	166 (12.5)	
ER expression			0.005
Negative	93 (23.0)	401 (30.2)	
Positive	312 (77.0)	926 (69.8)	
PR expression			0.007
Low	141 (34.8)	562 (42.4)	
High	264 (65.2)	765 (57.6)	
HER-2 expression			0.866
Low	205 (50.6)	683 (51.5)	
High	93 (23.0)	311 (23.4)	
Uncertain	107 (26.4)	333 (25.1)	
Ki-67 index			0.030
≤14%	59 (14.6)	256 (19.3)	
>14%	345 (85.2)	1066 (80.3)	
Histologic grade			<0.001
Low (level 1 or 2)	160 (39.5)	540 (40.7)	
High (level 3)	71 (17.5)	130 (9.8)	
Unknown	174 (43.0)	657 (49.5)	
Molecular typing			0.051
Luminal A	144 (35.6)	454 (34.2)	
Luminal B	80 (19.7)	217 (16.4)	
HER-2 enriched	41 (10.1)	177 (13.3)	
Triple negative	23 (5.7)	120 (9.0)	
Unknown	117 (28.9)	359 (27.1)	

US: Ultrasound; ER: Estrogen Receptor; PR: Progesterone Receptor; HER-2 : Human Epidermal Growth Factor Receptor 2; Luminal A: ER And/Or PR With Negative HER-2 And Low Ki-67 Index (≤14%); Luminal B: Subtype Is Identified As ER-Positive: HER-2-Negative And High Ki-67 Index (>14%) Or ER-Positive: HER2-Positive And Any Ki-67 Index; HER-2 Enriched: ER-Negative: PR-Negative And HER-2-Positive; Triple Negative: ER-Negative: PR-Negative And HER-2-Negative.

Table 2: Analysis of cumulative OS in ultrasound negative patients (ALNM≤3).

Group	1 year		3 year		5 year	
	FN	TN	FN	TN	FN	TN
Patients ≥50 years Events (n, %)	0 (131, 100)	12 (665, 98.2)	4 (131,96.9)	19 (665,97.1)	8 (131,93.6)	30 (665,95.0)
Early T-staging (≤2 cm) Events (n, %)	1 (156, 99.4)	6 (736, 99.3)	5 (156,96.8)	12 (736,98.6)	11 (156,92.8)	26 (736,95.8)
Low histologic (1 or 2) Events (n, %)	0 (128, 100)	6 (540, 98.9)	1 (128,99.2)	12 (540,97.8)	3 (128,99.7)	20 (540,95.8)
Ki-67 (≤ 14%) Events (n, %)	0 (52, 100)	1 (256, 99.6)	0 (52,100)	2 (256,99.2)	1 (52,98.1)	3 (256,98.4)

Table 3: Analysis of cumulative DFS in ultrasound negative patients (ALNM≤3).

Group	1-year		3-year		5-year	
	FN	TN	FN	TN	FN	TN
Patients ≥50 years Events (n, %)	0 (131,100)	11 (665,98.3)	6 (131,95.4)	24 (665,96.4)	13 (131,89.1)	39 (665,93.7)
Early T-staging (≤2 cm) Events (n, %)	2 (156,98.7)	8 (736,99.0)	5 (156,96.8)	18 (736,97.6)	13 (156,90.9)	38 (736,94.1)
Low histologic (1 or 2) Events (n, %)	0 (128,100)	7 (540,98.7)	4 (128,97.7)	15 (540,97.2)	8 (128,92.7)	29 (540,93.8)
Ki-67 (≤14%) Events (n, %)	0 (52,100)	2 (256,99,2)	0 (52,100)	5 (256,98.0)	1 (52,98.1)	7 (256,96.8)

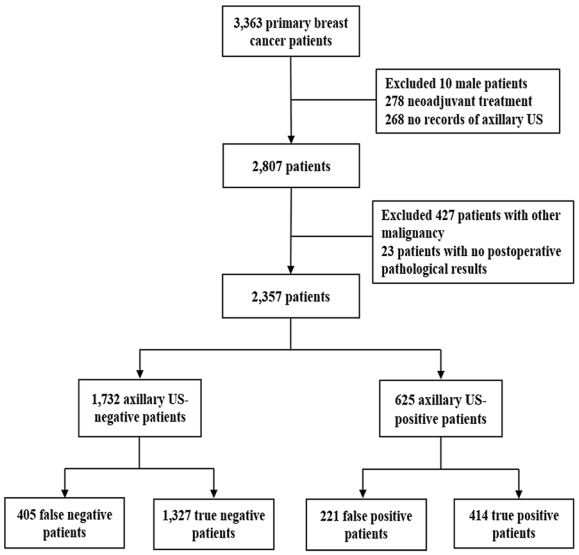

Figure 1: Flow chart of patients selection for final analysis..

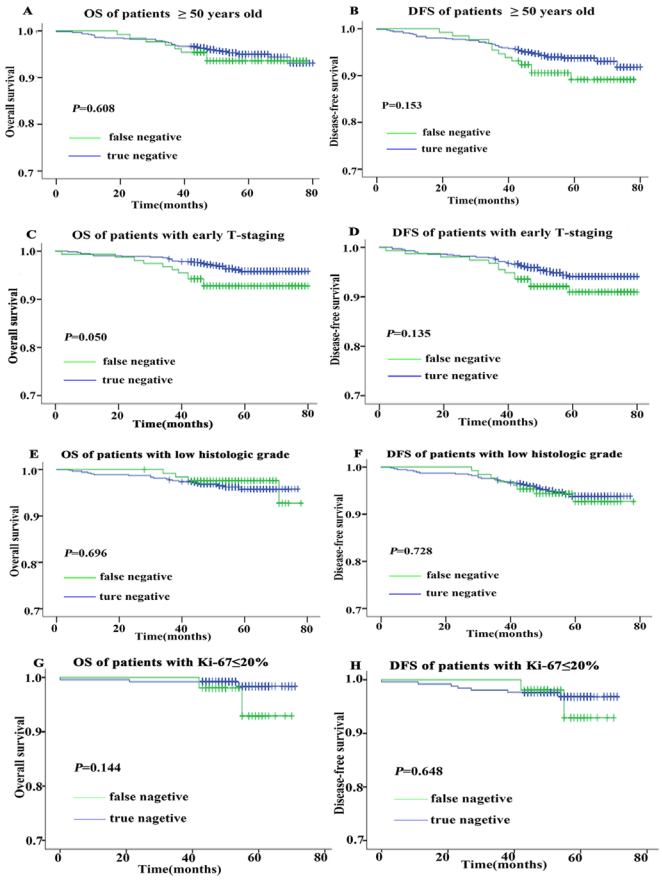

Figure 2: The OS and DFS of breast cancer patients with different clinicopathological characteristics.

Discussion

US with its simple, cheap, and widely available, has become one of the most important imaging methods for assessing the primary tumor and regional lymph nodes of breast cancer patients before surgery [15]. According to the literature, US can be highly specific if morphologic characteristics are used, with a sensitivity ranging from 26% to 76% and a specificity of 88%-98% for depicting nonpalpable metastatic lymph nodes. US-guided FNA has reported sensitivity, specificity, and negative predictive values of 35-65%, 68-78% and 79-97% respectively. US-guided CNB has a higher sensitivity, reaching 94% in some cases [16,17,18]. However, a negative FNA or CNB still does not remove the necessity of SLNB [18].

Traditionally, patients with invasive carcinoma of the breast underwent ALND to achieve accurate staging, regional control, and perhaps improved survival. However, with the advent of SLNB, an increasing number of people realize that the extent of operation necessary to cure for patients with early breast cancer is often excessive. The results of prospective studies in recent years are changing the view of axillary surgery. According to the Z0011 trial, more extensive surgery of the axilla does not provide an additional survival benefit or change the prognosis for early breast cancer patients [19]. Recent publications suggested that early disease patients with clinically and radiologically negative axillae do not require SLNB [14,20]. Thus, AUS is currently under the spotlight for its potential to reduce the need for SLNB. Chowdhury D et al. [21] reported that the false negative rates with AUS (10.7%) are comparable to that of SLNB (10%) in the clinically negative axilla in patients with early breast cancer. Therefore, the former can possibly replace the latter.

The role of AUS is currently being investigated by two clinical trials, SOUND and INSEMA. Patients were divided into the research group (patients with cT1N0 BC and a negative AUS to SLNB) and observation group (long-term ultrasound observation and no SLNB) to evaluate differences in OS, DFS, and quality of life [22-24]. While awaiting the results of these trials, SLNB for patients with early-stage breast cancer will remain the standard of care [25]. Moreover, as the false-negative rates of AUS (21%-48%) are not optimal, the demand for axillary surgery remains even if AUS is negative [26]. In patients with no lymph node found clinically, which patients would benefit most from AUS evaluation for metastatic disease? Our study analyzed the survival of patients with negative axillary lymph nodes diagnosed by preoperative ultrasound. We found that in the low-risk group (patients with older age, smaller primary tumor, lower expression of Ki-67 and lower histological grade), the proportion of patients with >3 axillary lymph nodes metastasis confirmed by postoperative pathology was extremely low (1.8% - 5.3%). Additionally, there was no significant difference

in the 5-year DFS and OS between the false negative and true negative group in low-risk patients. Even if the false negative rate existed, the prognosis of patients had no difference. Based on these findings, patients with a low likelihood of having axillary nodal metastasis, it is unlikely that omission of SLNB would change the prognosis. Thus, we maybe predict that the low-risk patients who have older age, smaller primary tumor, lower expression of Ki-67 and lower histological grade might avoid axillary surgery when US diagnosis is negative.

Our study has some limitations. This study involved patients managed almost 10-year period, with gradual adoption of the Z0011 criteria and as such there are some patients with no more than two positive SLNs who underwent ALND. Additionally, it is a retrospective study at a single center. Multicenter and prospective studies are required to confirm the conclusion.

Conclusions

On all these counts, our study provided that in false negative group, patients with advanced age, small tumor size, low expression of Ki-67 and low histological grade were at low risk of poor prognosis. Therefore, for this low-risk patients, preoperative US diagnosis of ALN is negative, which is expected to avoid ALN surgery.

Declarations

Acknowledgments: Not Applicable.

Funding: None.

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

Ethical statement: The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Fourth Hospital of Hebei Medical University (2021KY056), and individual consent for this retrospective analysis was waived.

Keywords: Breast cancer; Ultrasound; Lymph node metastasis; Prognosis.

Abbreviations: US: Ultrasound; AUS: Axillary Ultrasound; Alns: Axillary Lymph Nodes; ALNM: Axillary Lymph Node Metastasis; ALND: Axillary Lymph Node Dissection; SLN: Sentinel Lymph Nodes; SLNB: Sentinel Lymph Node Biopsy; DFS: Disease-Free Survival; OS: Overall Survival; Ki-67: Nuclear-Associated Antigen Ki-67; HER-2: Human Epidermal Growth Factor Receptor 2; DCIS: Ductal Carcinoma In Situ; LCIS: Lobular Carcinoma In Situ; ER: Estrogen Receptor; PR: Progesterone; HR: Hazard Ratio; CI: Confidence Intervals; NPV: Negative Predictive Value; FNA: Fine-Needle Aspiration; CNB: Coarse-Needle Biopsy.

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