The Value of Ultrasound Diagnosed Axillary Lymph Node in Avoiding Axillary Surgery in Early Breast Cancer Patients

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Abstract

Background: Axillary lymph node dissection can be avoided in early stage breast cancer patients with negative sentinel lymph node biopsy. However, the possibility of avoiding axillary surgery in patients without axillary lymph node metastasis (ALNM) by preoperative imaging is still under exploration. Thus, the objectives of this study were to investigate the high-risk factors of false negative of ALNM diagnosed by preoperative ultrasound (US) and to find out who could be avoided axillary surgery in the US negative ALNM patients.

Methods: This study retrospectively analyzed 3,361 patients with primary early breast cancer diagnosed in the Breast Center of the Fourth Hospital of Hebei Medical University from January 2010 to December 2012. All patients had undergone routine preoperative US and then axillary lymph node dissected. This study investigated the clinicopathological features of axillary lymph node (ALN) negative patients diagnosed by preoperative US and its correlation with prognosis. The follow-up data for disease-free survival (DFS) and overall survival (OS) were obtained from 2,357 patients.

Results: The sensitivity, specificity and accuracy of axillary US in this cohort were 66.24%, 76.62% and 73.87%. The proportion of patients in the false negative group was higher than that in true negative in the group of age < 50 years old ($P = 0.002$), tumor size > 2cm ($P = 0.008$), estrogen receptor (ER) positive ($P = 0.005$), progesterone receptor (PR) high expression ($P = 0.007$), nuclear-associated antigen Ki-67 (Ki-67) >20% ($P = 0.030$), visible vascular tumor thrombus ($P < 0.001$) and histological grade >2 ($P < 0.001$). Prognostic analysis of false negative and true negative ultrasonographic diagnosis of ALN metastasis: when ALNM was not found by preoperative ultrasound, there was no significant difference in patients with $ALNM \leq 3$ compared with patients without lymph node metastasis in patients of age ≥ 50 years old, tumor size ≤ 2 cm, Ki-67 $\leq 20\%$, or histological grade ≤ 2 .

Conclusion: The surgery of ALN may be avoided for the preoperative US diagnosed ALNs negative in early breast cancer patients who had advanced age, small tumor size, low expression of Ki-67 and low histological grade.

Background

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, 2]. The metastatic pathways of breast cancer include local invasion, lymphatic metastasis, and blood channel metastasis, among which ALNM is the earliest and most common form of breast cancer metastasis. Moreover, axillary lymph node status is one of the most important prognostic factors in breast cancer. Nowadays, the theory of molecular typing based on the characteristics of breast cancer gene expression and tumor morphology is accepted by most people [3–5]. But breast cancer has a high degree of heterogeneity in molecular typing, and the treatment sensitivity and prognosis of patients will also change. Therefore, it puts forward higher requirements for clinical imaging diagnosis [6, 7].

Many imaging modalities can be used to preoperatively evaluate ALN status, while the primary nonsurgical imaging modality for evaluating ALN is US. US is the best non-invasive method for evaluating ALNs and provides significant benefits compared with mammography and magnetic resonance imaging among patients with clinically node-negative breast cancer [8]. Several previous studies showed that preoperative axillary US had the sensitivity of 50–70% and specificity of 87–95%. However, as the false negative rates of US (21%-48%) are not optimal, the demand for axillary surgery remains even if US is negative [9, 10, 21].

Axillary lymph node dissection (ALND) is an important basis for lymph node staging after breast cancer surgery. Although it can completely remove metastatic or high-risk lymph nodes, it will not only cause upper limb pain and lymphedema, but also cannot improve local control and long-term survival of patients with ALNs negative. In the 1990s, the advent of sentinel lymph node biopsy (SLNB) made it possible for some patients to avoid ALND [11]. However, SLNB still carries morbidities, such as lymphedema and long term paresthesia. In addition, one study demonstrated that considering both cost and effectiveness, observation was superior to SLNB in postmenopausal women with cT1-T2 N0, HR+/HER2- breast cancer and negative axillary US [12]. The results of the Z0011 trial found that patients with early breast cancer and no more than two positive sentinel lymph nodes (SLNs) could be spared from ALND with no difference axillary disease recurrence and survival outcome [8, 32]. Furthermore, a large randomized, controlled, multi-center clinical trial SOUND (Sentinel node vs. Observation after axillary Ultra-sound) randomized patients who had the negative ALN assessed by preoperative US or single suspicious lymph node detected by US and negative by ultrasound-guided lymph node biopsy into two groups: SLNB ± ALND and long-term US observation. This ongoing study might prove patients not determined with lymph node on US avoiding SLNB in the future.

Therefore, in this study, we retrospectively analyzed the relationship between US evaluation ALN status and clinicopathological features and prognosis, which was helpful for providing a certain theoretical basis for the choice of breast cancer treatment options and the evaluation of its prognosis.

Methods

Patients

3,363 patients who were diagnosed as primary breast cancer at the Breast Center of the Fourth Hospital of Hebei Medical University from January 2010 to December 2012 were selected. All patients underwent preoperative US diagnosis and ALND. According to the screening criteria of this study, 1,005 cases were excluded, and 2,357 cases were enrolled (Fig. 1). The study was approved by the Scientific and the Ethics Committees of Fourth Hospital of Hebei Medical University (Hebei, China).

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 positive US axillary lymph nodes, and lymph nodes that did not meet any of those above signs of malignancy were recorded as negative US axillary lymph nodes.

Clinical and pathological data

ER, PR, human epidermal growth factor receptor 2 (HER-2) and Ki-67 are the routine pathological examination indexes of our hospital. According to the current diagnostic criteria, we reread pathological sections. ER was detected according to "Guidelines for Immunohistochemical Detection of Estrogen and Progesterone Receptors in Breast Cancer (2015 Edition)" of China. In our study, the positive threshold of ER immunohistochemical detection was $\geq 1\%$. The positive threshold of PR immunohistochemical detection was $\geq 1\%$. PR 20% positive was used as the cutoff value for Luminal A and Luminal B. In our study, whether PR $\geq 20\%$ was divided into high and low expression groups. Ki-67 20% was used as the cutoff for high and low expressions [20]. HER-2 was detected according to "Breast Cancer HER-2 Testing Guidelines (2014 Edition)" and "Concept for the Clinical Diagnosis and Treatment of Human Epidermal Growth Factor Receptor 2 Positive Breast Cancer 2016" of China. Tumors were graded using the modified Scarff-Bloom-Richardson grading system. Each score was from 1–3 points (good-bad), and the three types of scores are superimposed and divided into three levels: level 1 (3–5 points), level 2 (6–7 points), level 3 (8–9 points). In our study, the histological grade was divided into low group (level 1 or 2) and high group (level 3). 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.

We compared two groups (true negative and false negative) in terms of age (< 50 y and ≥ 50 y), size of the primary tumor (≤ 2 cm, > 2 cm), ER (negative and positive), PR (low and high), Ki-67 ($\leq 20\%$ and $> 20\%$), HER-2 (low and high), and histological grade of the primary tumor (low and high).

Follow-up

The number of follow-up visits was one to three. 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

Sensitivity was calculated as the proportion of patients with pathologic metastatic lymph nodes who had an abnormal axillary lymph node in preoperative ultrasound images. Specificity was calculated as the proportion of patients with no pathologic metastatic lymph node who had a normal lymph node in

preoperative ultrasound images. Accuracy was calculated as the proportion of patients whose axillary lymph node status was correctly predicted by ultrasound [13]. Statistical software was analyzed by SPSS 24.0 software, and $P < 0.05$ was set as statistically different. The clinicopathological characteristics (age, primary tumor size, ER expression) 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.

Results

Clinicopathological characteristics of false negative and true negative patients

A total of 2,357 breast cancer patients were enrolled in the final analysis, which including 1,732 US ALNs negative and 625 US ALNs positive patients. 405 (23.4%) were ALNs false negative and 1,327 (76.6%) were ALNs true negative (Fig. 1). The sensitivity, specificity and accuracy of preoperative ultrasonography in the diagnosis of ALNM were 66.24%, 76.62% and 73.87%, respectively. The follow-up time was 42 months to 80 months, and the median follow-up time was 58 months. 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).

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

False negative (n = 405)		True negative (n = 1,327)	
Characteristic	N %	N %	<i>P</i>
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			0.005
Negative	93 (23.0)	401 (30.2)	
Positive	312 (77.0)	926 (69.8)	
PR			0.007
Low	141 (34.8)	562 (42.4)	
High	264 (65.2)	765 (57.6)	
HER-2			0.866
Negative	205 (50.6)	683 (51.5)	
Positive	93 (23.0)	311 (23.4)	
Uncertain	107 (26.4)	333 (25.1)	
Ki-67 index			0.030
≤ 20%	59 (14.6)	256 (19.3)	
> 20%	345 (85.2)	1066 (80.3)	
Histologic grade			< 0.001
Low (1 or 2)	160 (39.5)	540 (40.7)	
High (3)	71 (17.5)	130 (9.8)	
Unknown	174 (43.0)	657 (49.5)	
Molecular typing			0.051

	False negative (n = 405)	True negative (n = 1,327)
Luminal A	144 (35.6)	454 (34.2)
Luminal B	80 (19.7)	217 (16.4)
HER-2+	41 (10.1)	177 (13.3)
Triple negative	23 (5.7)	120 (9.0)
Unknown	117 (28.9)	359 (27.1)

Prognostic analysis of US diagnosis of ALNM in false negative and true negative groups

Univariate analysis using the Kaplan-Meier method showed that the patients < 50 years old had worse OS and DFS in false negative group 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 (Fig. 2, Table 2, 3). Furthermore, in the primary tumor ≤ 2 cm ($P = 0.050$, $P = 0.135$), Ki-67 $\leq 20\%$ ($P = 0.144$, $P = 0.648$) 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 (Fig. 2, Table 2, 3). In addition, in the ≥ 50 years old, tumor ≤ 2 cm, Ki-67 $\leq 20\%$, and the low histologic grade group, patients with more than 3 lymph node metastases accounted for only 4.4%, 5.3%, 2.2% and 4.6% of the total, 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 a part of breast cancer patients.

Table 2
Analysis of cumulative OS in ultrasound negative patients (ALNM $\leq$ 3)

Group Events (n, %)	1-year		3-year		5-year	
	False	True	False	True	False	True
Age $\geq$ 50 years	0 (131,100)	12 (665,98.2)	4 (131,96.9)	19 (665,97.1)	8 (131,93.6)	30 (665,95.0)
Tumor $\leq$ 2 cm	1 (156,99.4)	6 (736,99.3)	5 (156,96.8)	12 (736,98.6)	11 (156,92.8)	26 (736,95.8)
Histologic grade (1 or 2)	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 $\leq$ 20%	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 $\leq$ 3)

Group Events (n, %)	1-year		3-year		5-year	
	False	True	False	True	False	True
Age $\geq$ 50 years	0 (131,100)	11 (665,98.3)	6 (131,95.4)	24 (665,96.4)	13 (131,89.1)	39 (665,93.7)
Tumor $\leq$ 2 cm	2 (156,98.7)	8 (736,99.0)	5 (156,96.8)	18 (736,97.6)	13 (156,90.9)	38 (736,94.1)
Histologic grade (1 or 2)	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 $\leq$ 20%	0 (52,100)	2 (256,99.2)	0 (52,100)	5 (256,98.0)	1 (52,98.1)	7 (256,96.8)

Discussion

With the development of technology, many imaging modalities can be used to preoperatively evaluate ALN status, such as mammography, computed tomography, and magnetic resonance imaging. But 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 [14]. In

our retrospective study, we evaluated the clinicopathologic factors associated with the false negative US results and the effect of false negative on prognosis. Our data showed that US had 66.24% sensitivity, 76.62% specificity and 73.87% overall accuracy in the diagnosis of breast cancer axillary lymph metastases, which were consistent with the reported data [15–17]. According to the literature, a normal lymph usually shows as a reniform shape, uniformly hypoechoic cortex with a maximal thickness less than 3 mm, smooth margins, and intact central fatty hilum [18]. On the contrary, suspicious findings of ALN are cortical thickness greater than 2.5–3.0 mm, focal cortical lobulation, loss of the fatty hilum, a round shape, and abnormal cortical blood flow [19]. Kuna SK suggested that the short diameter of lymph nodes > 0.5 cm should be used as the index of judging the pathological lymph nodes, and especially when the short diameter > 1 cm, it should be suspected to be malignant [20]. Most scholars regarded the L/T ratio of lymph nodes equal to 2 as the dividing point of benign and malignant lymph nodes. In most studies, the thickness of lymph node cortex was 3.0 mm as the dividing point between benign and malignant, but the results of accuracy, sensitivity and specificity were different respectively [21–23]. In 2008, Bedi et al. proposed the 6 classification of lymph node cortex morphology, which was accepted by many mathematicians. Because the accuracy of ALN evaluation by this standard was relatively high (80%) [24]. Although there is no guide or consensus for lymph node assessment on US, these are the imaging methods upon which the majority of diagnoses in daily practice relies.

In our study, the false negative rate of axillary ultrasound was 23.4%, which was within the ranges of previous studies in Western countries [25]. Additionally, we analyzed the histopathological and tumor characteristics associated with false negative axillary ultrasonography results. A retrospective study conducted by Park et al. pointed out that positive expression of ER and PR was associated with a high false negative rate of US [26]. While, Yan' na Zhang et al. [13] believed that the level of hormone receptor affected the accuracy of ultrasound diagnosis. This might be explained by the fact that ER/PR-positive breast cancer usually involves large tumors without clinically significant axillary metastases. We retrospectively analyzed the pathological data of 2,357 patients and found that ER-positive and high expression of PR (> 20%) could lead to a higher rate of false negative. Furthermore, we found that the difference of molecular typing might affect the false negative rate, and from high to low were luminal B, luminal A, HER-2 and triple negative. Compared with HER-2 and triple negative breast cancer patients, the high false negative rate of luminal A or luminal B might be due to the positive hormone receptor. In addition, our data indicated that false negative patients were more likely to occur in younger than 50 years old, Ki-67 high expression (> 20%), larger primary tumor size (> 2 cm) and higher histological grade, which was consistent with the results of Yan' na Zhang and other studies [27]. Therefore, in the high-risk subgroups that can lead to high false negative rate, we should carefully consider the results of ultrasound, and combine other examination methods, such as various kinds of tumor puncture biopsy, to improve the accuracy of preoperative diagnosis [28–31].

Because of false negative rate, even if axillary ultrasonography is negative, axillary surgery is still needed, such as SLNB and ALND. However, the Z0011 trial have modified the indication for ALND, and patient with no more the two positive SLNs could be spared from ALND [32]. A retrospective analysis of 355 cases of pT1 breast cancer showed that axillary ultrasound had moderate sensitivity in T1 tumor.

Therefore, ALND was not needed in all patients with axillary involvement. Axillary ultrasound and fine needle puncture could predict axillary involvement, thus avoiding SLNB [33, 34]. Can SLNB be avoided in breast cancer patients with US negative ALNs? This question was attempted to answer in the clinical trial of SOUND. In this trial, the distant disease-free survival (DDFS), DFS and axillary recurrence, etc. of both in the research group (SLNB ± ALND) and observation group (long-term ultrasound observation) had extremely low number of events, which might prove some low-risk patients could avoid SLNB [35, 36]. In a trial of patients aged 65–80 years with cT1N0M0 disease randomized to ALND versus no axillary surgery, researchers found no survival difference between the groups, and a 5-year axillary recurrence rate of only 1.8% in the no ALND group [34]. The study of Chowdhury D showed that the false negative rate of US and SLNB are comparable, the former could possibly replace the latter, at least in a subset of early breast cancer patients [37]. 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 with older age, smaller primary tumor, lower expression of Ki-67 and lower histological grade might avoid axillary surgery when US diagnosis is negative.

Conclusions

There was no significant difference in the 5-year DFS and OS between the false and true negative group in low-risk patients. Therefore, in the above subgroups, if the preoperative US diagnosis is negative, there might be a possibility of avoiding axillary surgery. However, when ultrasound can be used to directly predict the prognosis, it still needs more data and longer follow-up time.

Abbreviations

US

ultrasound; ER:estrogen receptor; PR:progesterone receptor; HER-2:human epidermal growth factor receptor 2; Ki-67:nuclear-associated antigen Ki-67; ALNM:axillary lymph node metastasis; ALN:axillary lymph node; disease-free survival; overall survival; SLNB:sentinel lymph node biopsy

Declarations

Competing interests

The authors declare that they have no competing interests.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Ethics approval was obtained from the Scientific and the Ethics Committees of Fourth Hospital of Hebei Medical University, and written informed consent was obtained from study participants.

Authors' contributions

Contributed substantially to study conception and design, data acquisition, data analysis and interpretation: ZCS, NL, LY. Participated in collecting data and drafted the manuscript: NL, LY. Partially collected data and performed the statistical analysis: WXL, WMQ, LRY. All authors read and approved the final manuscript.

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Consent for publication

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Figures

Figure 1

Flow chart of patient selection for final analysis.

Figure 2

There was no significant difference in DFS and OS between the false negative and true negative US group. A and B Kaplan-Meier curves of OS and DFS in breast cancer patients older than 50 years old. C and D Kaplan-Meier curves of OS and DFS in early T-staging patients ($T \leq 2\text{cm}$). E and F Kaplan-Meier curves of OS and DFS in low histologic grade patients. G and H Kaplan-Meier curves of OS and DFS in patients with $\text{Ki-67} \leq 20\%$.