Original Article

Relationship of Sonographic Tumor Size and Grading of Invasive Ductal Carcinoma; Not Otherwise Specified (IDC; NOS) of Breast Cancer on Axillary Nodal Metastasis

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Abstract

Introduction: Axillary nodal involvement is an essential prognostic factor in patients with breast cancer. Both mammogram and ultrasound are used for preoperative axillary nodal staging. Increasing pathological tumor size and higher tumor grade are significantly associated with an increased risk of axillary lymph node metastasis. Our objective was to evaluate the relationship between sonographic tumor size and grading of invasive ductal carcinoma; not otherwise specified (IDC; NOS) of breast cancer and axillary nodal metastasis.

Method: A retrospective review to all patients with cytology-proven IDC; NOS at Thammasat University Hospital (TUH) from January 2013 to June 2017. To evaluate the relationship of sonographic tumor size and grading on axillary nodal metastasis, we constructed multivariable logistic regression models adjusted for age, tumor size and tumor grading.

Result: Total 204 eligible patients, 118 (57.8%) were positive axillary lymph node status. In comparison, tumor size was larger in positive axillary lymph node status patients; median 25 mm (min 10 - max 117 mm) vs 20 mm (min 5 - max 60 mm), $P = 0.001$. Larger tumor size was associated with more axillary lymph node metastasis (adjusted odds ratio 1.49, 95% confidence interval; 1.11-1.91, $P = 0.002$). For tumor grading, there was no significantly associated with axillary lymph node metastasis.

Conclusion: Sonographic tumor size can be used as a predictive value in breast cancer. Larger tumor of IDC; NOS was associated with more axillary lymph node metastasis.

Keywords: Breast cancer, Axillary lymph node metastasis, Tumor size, Tumor grading

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Introduction

Invasive ductal carcinoma (IDC) is the most common type of breast cancer, accounting for approximately 80% of all invasive breast cancer.[1] There are the different types of histological appearances in IDC, the most common feature called "Not Otherwise Specified" (NOS).[2]

In patients with breast cancer, the cancer cells most likely spread to the axillary lymph nodes first. Increased number of metastatic axillary lymph nodes is associated with increased chance of recurrence and mortality.[3, 4] Consequently, the nodal status plays a significant role in treatment decision including surgery, systemic adjuvant chemotherapy or locoregional irradiation. For these reasons, axillary nodal involvement is an essential prognostic factor.

For preoperative axillary nodal staging, Currently, both mammogram and ultrasound (US) are initially used for pre-operative nodal staging. If abnormal lymph nodes are found, this indicates the need for pathological samplings such as fine-needle biopsy (FNA) or core-needle biopsy (CNB). If lymph nodes appear unremarkable or FNA/CNB result is negative, then sentinel lymph node biopsy (SLNB) is considered.

Every lymph node-positive result should be confirmed with conventional axillary lymph node dissection (ALND), which is considered the gold standard for nodal staging. However, compared with SLNB, ALND is associated with significantly higher morbidity such as pain, sensory disturbance, paresthesia, seroma, infection, shoulder stiffness, and lymphedema of the arm.[5, 6]

Due to a variety of clinical course of breast cancer, identification of prognostic factors is essential for predicting clinical course and response to specific treatment protocols result in the best outcomes of patients.

Histologic grade nuclear components of Scarff-Bloom-Richardson (SBR) in patients with IDC found that higher SBR grade was associated with higher recurrence than lower grade.[7]

Several studies reported that increasing size of the tumor and higher tumor grade were significantly associated with an increased risk of axillary lymph node metastasis.[8, 9, 10, 11, 12]

Size of the tumor in previous studies was commonly acquired from pathological examination following surgery. Ultrasound is an available bedside test with a short time of scan and no safety concerns. There are limited data in the tumor size measured by US, so we sought to examine the relationship of sonographic tumor size and grading of IDC on axillary nodal metastasis.

Method

The study was approved by the human ethics committee of Thammasat University.

We conducted a retrospective review to all patients with cytology-proven invasive ductal carcinoma; not otherwise specified (IDC; NOS) at Thammasat University Hospital (TUH) from January 2013 to June 2017. Patient's data were retrieved from the medical records, including imaging data from Picture Archiving and Communication System (PACS). The data were patient's age, sonographic tumor size, Scarff-Bloom-Richardson (SBR) tumor grading and axillary lymph node status of metastasis. All data were collected manually in case-record form.

All US images were re-measured the tumor size (defined as the longest diameter of the tumor, the imaging plane in which the lesion appeared longest was chosen) (Figure 1) by two radiologists, whom were blinded to the patient's data, and agreed by consensus.

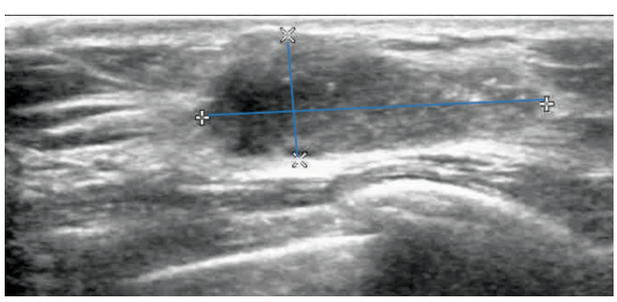

Figure 1 A 43-year-old female with invasive ductal carcinoma; not otherwise specified (IDC; NOS) grade 3. Two measurements were performed perpendicular to each other.

Areas of posterior shadowing and partial voluming were carefully excluded from the measurement. Lesions of larger size compared to the footprint of the probe required use of wide scan and panoramic setting.

Study population

Inclusion criteria were cases that had cytology-proven NOS type of invasive ductal carcinoma (IDC), underwent US (SAMSUNG® RS80A and PHILIPS® IU22) and had images in PACS of Thammasat University Hospital.

Patients were excluded if no axillary nodal histological data, received neo-adjuvant treatment, had previous or concomitant malignancy, recurrent breast cancer or histological types other than NOS.

Statistical analyses

Baseline patient characteristics were analyzed by using descriptive statistics and were compared by using the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

To evaluate the relationship of sonographic tumor size and grading of IDC; NOS of breast cancer on axillary nodal metastasis, we constructed multivariable logistic regression models; setting a significant level at 0.05 ($P < 0.05$). Statistical analyses were performed with STATA software (version 14.0; StataCorp, College Station, TX).

Result

From all 268 invasive breast cancer patients, 64 were excluded from our study due to no axillary nodal histological data (27), received neo-adjuvant treatment (17), had previous or concomitant malignancy (6), recurrent breast cancer (5) and histological types other than NOS (9). Total eligible subjects enrolled were 204 (118 were Positive nodal status).

Mean patient's age was 55.1 with standard deviation 12.4 (range 21 to 88 years). Tumor size was divided in to 6 groups as follows: group I <10 mm, group II 10 - 20 mm, group III 21 - 30 mm, group IV 31 - 40 mm, group V 41 - 50 mm and group VI > 50 mm. Distribution of patients based on tumor size was presented in Figure 2 and tumor characteristics were summarized in Table 1. The most grade of tumor was 2 (about 50%).

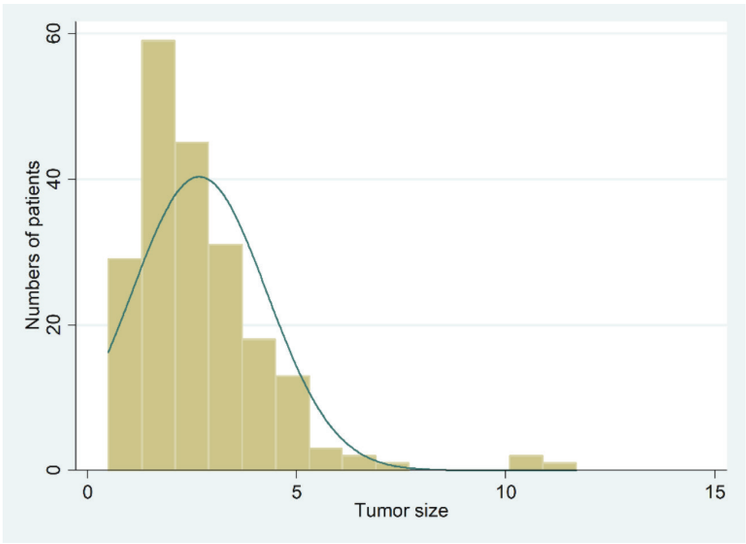

Figure 2 Distribution of patients based on tumor size.

Table 1 Tumor characteristics

Characteristics	Numbers of patients (%)
Tumor size (mm)	
I. < 10	16 (7.8)
II. 10 - 20	66 (32.4)
III. 21 - 30	64 (31.4)
IV. 31 - 40	29 (14.2)
V. 41 - 50	17 (8.3)
VI. > 50	12 (5.9)
Tumor grading	
1	19 (9.3)
2	102 (50.0)
3	83 (40.7)

Relationship between sonographic tumor size and axillary lymph node metastasis shows in Table 2. There were 86 (42.2%) negative axillary lymph node status patients and 118 (57.8%) positive ones. In comparison, sonographic tumor size was significantly larger in positive axillary lymph node status patients; median 25 mm (min 10 - max 117 mm) versus 20 mm (min 5 - max 60 mm), $P = 0.001$. In addition, tumor size in pre-classified 6 groups was significant difference between two groups of axillary lymph node status ($P < 0.001$). However, there was no significant difference in tumor grading between two groups ($P = 0.429$) as shown in Table 3.

Table 2 Relationship between sonographic tumor size and axillary lymph node metastasis

	Patients nodal status				*P* - value
	Negative (N = 86)		Positive (N = 118)		
	N	%	N	%	
Tumor size (mm)					< 0.001
< 10	14	87.5	2	12.5	
10 - 20	31	47.0	35	63.0	
21 - 30	23	35.4	42	64.6	
31 - 40	7	24.1	22	75.9	
41 - 50	9	52.9	8	47.1	
> 50	2	16.7	10	83.3	

Table 3 Relationship between tumor grading and axillary lymph node metastasis

	Patients nodal status				*P*-value
	Negative (N = 86)		Positive (N = 118)		
	N	%	N	%	
Tumor grading					0.429
1	8	38.9	11	61.1	
2	45	44.1	57	55.9	
3	33	39.8	50	60.2	

Table 4 shows results from multivariable logistic regression analysis of factors associated with axillary lymph node metastasis (adjusted with age, tumor size in 6 groups and tumor grading). Larger tumor was associated with more axillary lymph node metastasis (adjusted odds ratio 1.49, 95% confidence interval; 1.11-1.91, $P = 0.002$). For tumor grading, there was no significantly associated with axillary lymph node metastasis.

Table 4 Results from multivariable logistic regression analysis of factors associated with axillary lymph node metastasis*

Associated factor	Adjusted Odds ratio	95% confidence interval	*P* - value
Tumor size in 6 groups	1.49	1.11 - 1.91	0.002
Tumor grading			
1	Ref	Ref	Ref
2	0.87	0.31 - 2.39	0.780
3	0.76	0.26 - 2.19	0.612

*Adjusted with age, tumor size in 6 groups, tumor grading

As shown in table 2, the percentage of negative axillary lymph node status patients was highest in patients with sonographic tumor size below 10 mm compare to other groups. In consequence, we performed subgroup analysis in patients with sonographic tumor size below 10 mm compare with 10 mm and over using multivariable logistic regression analysis (Table 5). The result showed that sonographic tumor size 10 mm and over was highly associated with axillary lymph node metastasis (adjusted odds ratio 11.43, 95% confidence interval; 2.50 - 52.32, $P = 0.002$).

Table 5 Subgroup analysis in patients with sonographic tumor size below 10 mm and ≥10 mm; result from multivariable logistic regression analysis of factors associated with axillary lymph node metastasis*

Associated factor	Adjusted Odds ratio	95% confidence interval	*P* - value
Tumor size in 2 groups (mm)			
< 10	Ref	Ref	Ref
≥ 10	11.43	2.50 - 52.32	0.002
Tumor grading			
1	Ref	Ref	Ref
2	0.79	0.27 - 2.31	0.672
3	0.84	0.28 - 2.50	0.755

*Adjusted with age, tumor size in 2 groups, tumor grading

Discussion

Currently, the role of surgical management for breast cancer has been changed more conservatively than former radical mastectomy as well as the application of neoadjuvant chemotherapy before locoregional control. This indicates the importance of prognosis factors recognition at the time of diagnosis to predict clinical outcome with the administration of treatment.[12] Regional lymph node status is necessary for tumor staging and surgical planning. SLNB is now becoming a standard procedure in clinically node-negative patients, resulting in fewer surgical complications than conventional ALND.[11]

Previous evidence indicates that tumor size measured by ultrasound correlates well with pathological measures.[13, 14, 15, 16] Some authors reported a degree of underestimation for invasive

duct carcinoma; mean difference 0.30 ± 0.84 cm[17], 0.33 cm[18] and median difference 0.25 cm (0.15 - 0.35 cm) for ductal pattern.[19] Therefore, pathologic tumor size can be estimated from the ultrasonographic measurement.

The results from our study showed that larger sonographic tumor size was associated with axillary lymph node metastasis. In the same way to the previous study using tumor size by pathological measures; breast cancer with larger diameter had a greater metastatic potential.[9, 10, 11, 12] Rivadeneira et al. reported that increasing size of the tumor was significantly associated with an increased risk of axillary lymph node metastasis and was demonstrated for each 1-mm increase in size.[8]

Only 12.5% of patients with tumor size less than 10 mm had lymph node metastases. In contrast, more than 50% of patients with tumor size 10 mm and over had lymph node metastases. The result from subgroup analysis showed that patients with tumor size 10 mm and over were highly associated with axillary lymph node metastasis. Rate of axillary nodal metastasis has increased with tumor size increasing. This result may be explained by the larger tumor has been present longer and has more chance for metastasis.

In our study, tumor grading was not associated with axillary lymph node metastasis. Our result was inconsistent with the previous study of Le Doussal et al. These authors found that the patients with an SBR score of 3, compared with SBR score of 1, had a relative risk of nodal metastasis rate of 4.4.[7]

Conversely, the study of Velanovich et al. found a direct correlation between higher nuclear grade and tumor size. In addition, when controlling for tumor size with multivariate analysis, nuclear grade was not associated with lymph node metastasis.[20] Similarly to P.G. Gill et al. found that in 2,135 women with breast cancer, tumor grading was predictive of node involvement in the univariate analysis but it did not contribute to the multivariable model.[21] Thereby, those tumor grade correlation may result from others associated factor.

There were some limitations in this study. First, there was disproportionate ratio of case based on tumor grading. Few lesions were low histology grade compare to medium and high histologic grades (9.3%, 50.0%, and, 40.7% respectively). Second, This study was retrospectively performed at a single institution. We suggest that prospective multicenter clinical trials will be needed to validate the usefulness of the sonographic tumor size as a predictive value for metastatic potential.

Sonographic tumor size can be used as a predictive value in breast cancer. Larger tumor of invasive ductal carcinoma; not otherwise specified (IDC; NOS) of breast cancer was associated with axillary lymph node metastasis.

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Disclosure

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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