ความสัมพันธ์ของตำแหน่งก้อนมะเร็ง และระยะห่างของก้อนมะเร็งกับผิวหนัง ต่อการแพร่กระจายไปต่อมน้ำเหลืองที่รักแร้ของมะเร็งเต้านม

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บทคัดย่อ

มะเร็งเต้านมเป็นมะเร็งที่พบมากที่สุดในผู้หญิง การแพร่กระจายไปต่อมน้ำเหลืองที่รักแร้ในมะเร็งเต้านมนั้นเป็นปัจจัยพยากรณ์โรคที่สำคัญ โดยหากมีจำนวนการแพร่กระจายไปต่อมน้ำเหลืองที่รักแร้มากขึ้น พบว่ามีความสัมพันธ์กับการเสียชีวิต และการกลับเป็นซ้ำของโรคที่สูงขึ้น ซึ่งการระบายน้ำเหลืองของเต้านมเกิดขึ้นผ่านเส้นทางน้ำเหลืองใต้ลานหัวนมและผิวหนัง การศึกษานี้จึงมีสมมติฐานว่าก้อนมะเร็งที่อยู่ใกล้ผิวหนังมากขึ้นหรือตำแหน่งก้อนมะเร็งที่อยู่บริเวณใต้ลานนมจะมีการแพร่กระจายไปยังต่อมน้ำเหลืองที่รักแร้ได้มากกว่า เพื่อเป็นแนวทางในการรักษามะเร็งเต้านมต่อไป อย่างไรก็ตาม ข้อมูลการศึกษาเกี่ยวกับความสัมพันธ์ของระยะห่างของก้อนมะเร็งกับผิวหนังต่อการแพร่กระจายไปต่อมน้ำเหลืองที่รักแร้นั้นมีจำกัด การวิจัยเชิงพรรณนาย้อนหลังครั้งนี้มีวัตถุประสงค์ เพื่อศึกษาความสัมพันธ์ของตำแหน่งก้อนมะเร็ง และระยะห่างของก้อนมะเร็งกับผิวหนัง ต่อการแพร่กระจายไปต่อมน้ำเหลืองที่รักแร้ของมะเร็งเต้านม ในผู้ป่วยมะเร็งเต้านมที่ได้รับการวินิจฉัยและเข้ารับการรักษาในโรงพยาบาลพระจอมเกล้า จังหวัดเพชรบุรี ระหว่างวันที่ 1 มิถุนายน 2563 ถึง 30 มิถุนายน 2567 ทำการวิเคราะห์ข้อมูลโดยใช้สถิติการวิเคราะห์การถดถอยลอจิสติก มีผู้ป่วยมะเร็งเต้านม 200 คนได้รับการคัดเลือกเข้ามาสู่การศึกษา โดยผู้ป่วย 102 คน คิดเป็นร้อยละ 51 มีการแพร่กระจายไปยังต่อมน้ำเหลืองที่รักแร้ ผลการศึกษาพบว่าตำแหน่งใต้ฐานนม (subareolar region) มีความสัมพันธ์กับการแพร่กระจายของมะเร็งไปยังต่อมน้ำเหลืองที่รักแร้มากขึ้น เทียบกับตำแหน่งด้านใน (adjusted odds ratio=13.82, ความเชื่อมั่นร้อยละ 95=1.59-119.51, p=0.017) แต่ระยะห่างของก้อนมะเร็งกับผิวหนังไม่มีความสัมพันธ์กับการแพร่กระจายไปยังต่อมน้ำเหลืองที่รักแร้ โดยสรุป ตำแหน่งของก้อนมะเร็งจากการตรวจด้วยคลื่นเสียงความถี่สูงเต้านม สามารถใช้เป็นปัจจัยพยากรณ์การแพร่กระจายไปต่อมน้ำเหลืองที่รักแร้ได้ โดยตำแหน่งใต้ฐานนมมีความสัมพันธ์กับการแพร่กระจายไปยังต่อมน้ำเหลืองบริเวณรักแร้ที่มากขึ้น

คำสำคัญ: มะเร็งเต้านม; การแพร่กระจายของมะเร็งไปยังต่อมน้ำเหลืองบริเวณรักแร้; ระยะห่างผิวหนัง; ตำแหน่ง

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Association between tumor location, tumor-to-skin distance, and axillary lymph node metastasis in breast cancer

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Abstract

Breast cancer is the most commonly diagnosed cancer in women. Axillary lymph node metastasis (ALNM) is an essential prognostic factor, as a higher number of metastatic lymph nodes is associated with increased mortality and recurrence rates. The majority of lymphatic drainage from the breast occurs via dermal and subareolar plexuses. This study hypothesized that tumors located closer to the skin or within the subareolar region may have a higher propensity for ALNM via lymphatic pathways. These findings could guide future treatment strategies for breast cancer. However, only a limited number of studies have explored this hypothesis. This study was conducted a retrospective review of invasive breast cancer patients diagnosed and treated at Phrachomklao Hospital, Phetchaburi Province, from June 1, 2020, to June 30, 2024. Bivariate and multivariate logistic regression analyses were performed to evaluate the relationship between tumor location and tumor-to-skin distance with ALNM. Of the 200 eligible patients, 102 patients (51%) had positive axillary lymph node status. The analysis revealed tumors located in the subareolar region were significantly associated with an increased likelihood of ALNM (adjusted odds ratio=13.82, 95% confidence interval=1.59-119.51, p=0.017). However, the tumor-to-skin distance did not show a statistically significant relationship with ALNM. In summary, sonographic tumor location can serve as a prognostic factor for ALNM. Specifically, tumors located in the subareolar region are significantly associated with an increased likelihood of ALNM.

Keywords: breast cancer; axillary lymph node metastasis; tumor-to-skin distance; tumor location

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Introduction

Breast cancer is the most prevalent cancer among women worldwide[1]. Axillary lymph node metastasis (ALNM) is a key prognostic factor. An increased number of lymph node metastases is associated with a higher risk of mortality and disease recurrence[2,3]. The axillary nodal status plays a critical role in guiding treatment decisions. Preoperative prediction of ALNM is essential for determining appropriate treatment for patients, including surgical treatment options, chemotherapy or radiation[4].

The ACOSOG Z0011 trial[5] demonstrated that axillary lymph node dissection (ALND) did not significantly affect disease-free or overall survival in early-stage breast cancer patients (T1 and T2) with less than three positive sentinel lymph nodes who were treated with breast-conserving surgery (BCS), had undergone planned postoperative radiation therapy, and had not received neoadjuvant chemotherapy. Data from various studies suggest that patients with metastasis in one or two sentinel lymph nodes may be candidates for omitting ALND[6-10]. As a result, the management of early-stage breast cancer is shifting towards less frequent use of ALND, aiming to minimize complications and improve quality of life without adversely affecting recurrence rates and patient survival.

Various clinical, pathological, and molecular factors have been associated with the likelihood of ALNM. Consequently, several institutions have developed nomograms to aid in the prediction of ALNM. These nomograms utilize a variety of variables, including tumor size, patient age, tumor location, histological type, tumor grade, lymphovascular invasion, and hormone receptor status (estrogen receptor and progesterone receptor). However, they do not account for the distance between the tumor and the skin surface in their predictive models[11-13].

The majority of lymphatic drainage from the breast occurs via the cutaneous lymphatic system, which consists of a superficial plexus of channels within the dermis and a deeper network that runs alongside the mammary ducts in the subareolar region[14-19]. We hypothesize that primary breast cancers located closer to the rich lymphatic plexus in the dermal and subareolar areas may have greater access to these lymphatic networks, potentially increasing the risk of ALNM. However, only a limited number of studies have explored this hypothesis. Few studies have examined the relationship between the distance of primary breast cancer from the skin surface and the likelihood of ALNM. Ultrasonography (U/S) provides an accurate method for measuring this distance[20].

The objective of this study is to evaluate the association between sonographic tumor location, tumor-to-skin distance, and axillary lymph node metastasis in breast cancer patients.

Materials and Methods

The study was approved by the Human Ethics Committee of Phrachomklao Hospital, Phetchaburi Province.

This is a retrospective review of 200 patients with invasive breast cancer who

underwent preoperative breast ultrasound and subsequent breast and axillary surgery (ALND or sentinel lymph node biopsy) at Phrachomklao Hospital, Phetchaburi Province, from June 2020 to June 2024.

Study population

Inclusion criteria were limited to cases with a primary diagnosis of invasive breast cancer, documented axillary nodal histological data, preoperative breast ultrasound (performed using TOSHIBA Xario 200 and TOSHIBA Xario XG), and images stored in the hospital's picture archiving and communication system (PACS).

Patients were excluded if they had received neoadjuvant chemotherapy, had male breast cancer, had multifocal breast cancer, had a history of previous or concomitant malignancies, had recurrent breast cancer, or had been diagnosed with inflammatory breast cancer.

Abstraction of clinical and other data

Patient data, including imaging data from PACS, were retrieved from medical records. The collected information included patient age, tumor size, tumor location, tumor-to-skin distance, Scarff-Bloom-Richardson (SBR) tumor grade, hormone receptor status and axillary nodal status. All data were collected manually using case-record forms.

Tumor-to-skin distance was defined as the perpendicular distance from the most anterior hypoechoic edge of the tumor to the overlying skin surface (transducer face), as visualized in the ultrasound image. Measurements were obtained by two radiologists, blinded to axillary nodal status, and final values were agreed upon by consensus (Figure 1).

The location of the tumor in the breast was categorized as medial, lateral, overlapping, or subareolar (Figure 2).

Statistical analyses

Baseline patient characteristics were analyzed using descriptive statistics and compared using the chi-square test. Variables significantly associated with axillary lymph node metastasis (ALNM) in univariate analysis were subsequently entered into a multivariate logistic regression model using forward Wald selection method. Multicollinearity was assessed prior to model inclusion, and statistical significance was set at $p<0.05$.

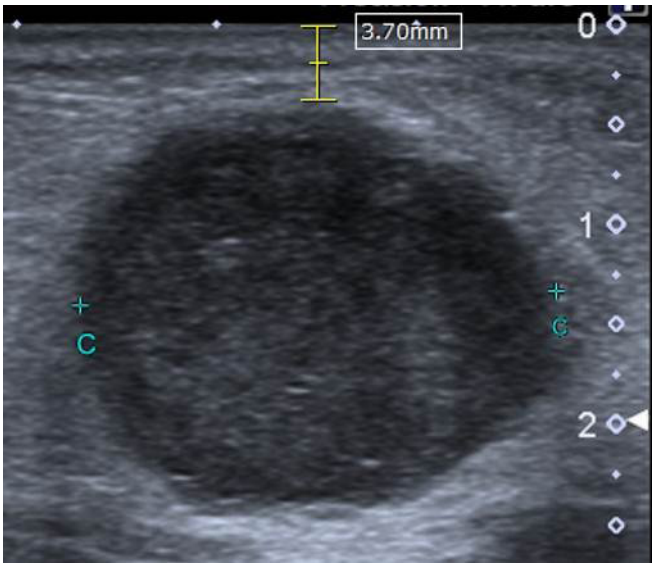

Figure 1 Ultrasonographic tumor-to-skin distance measurement

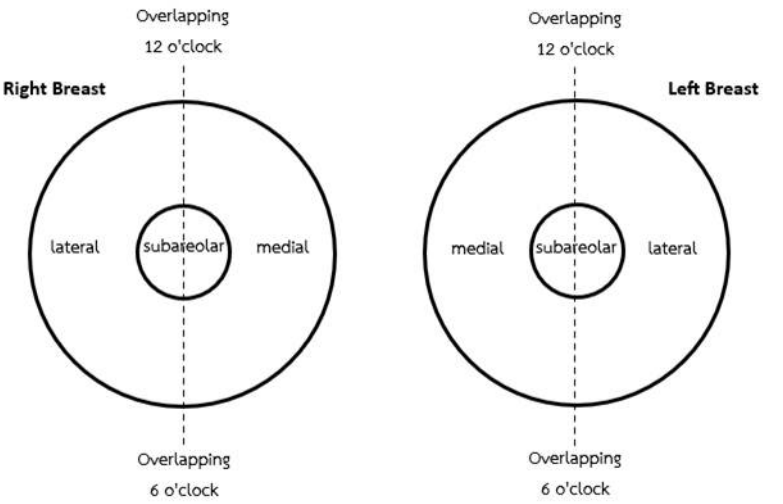

Figure 2 The location of the tumor in the breast

Results

Data were collected from 200 eligible breast cancer patients, of whom 98 (49%) were node-negative and 102 (51%) were node-positive. The descriptive characteristics of the study population are presented in Table 1.

The study results indicate a significant association between tumor location and ALNM (p=0.021). Of the 12 tumors located in the subareolar region, 11 cases (91.7%) exhibited ALNM, while only one case (8.3%) did not. Additionally, tumor size was significantly

associated with ALNM (p=0.010). However, tumor-to-skin distance, age, tumor grade, estrogen receptor (ER) status, progesterone receptor (PR) status, and HER2 receptor status did not show a significant association with ALNM, as detailed in Table 2.

Table 1 Descriptive clinicopathologic characteristics of 200 patients

Characteristic	Frequency	(%)
Age (years)		
≤50	69	(34.5)
>50	131	(65.5)
$\overline{X}$ = 56.31 S.D. 11.95		
Tumor location		
Medial	39	(19.5)
Lateral	127	(63.5)
Overlapping	22	(11.0)
Subareolar	12	(6.0)
Tumor-to-skin distance (mm)		
≤5	114	(57.0)
5.1-10	75	(37.5)
10.1-15	11	(5.5)
$\overline{X}$ = 4.95 S.D. 2.88		
Tumor size (mm)		
≤10	9	(4.5)
11-20	62	(31.0)
21-30	73	(36.5)
31-40	37	(18.5)
41-50	13	(6.5)
>50	6	(3.0)
$\overline{X}$ = 26.34 S.D. 12.23		
Tumor grade		
1	10	(5.3)
2	109	(57.4)
3	71	(37.4)
ER		
Negative	59	(30.9)
Positive	132	(69.1)
PR		
Negative	88	(46.1)
Positive	103	(53.9)

Table 1 Continued

Characteristic	Frequency	(%)
HER2		
Negative	97	(50.8)
Positive	45	(23.6)
Equivocal	49	(25.7)

Bivariate and multivariate logistic regression analyses revealed that tumors located in the subareolar region were associated with a significantly higher likelihood of ALNM compared to those in the medial region (adjusted odds ratio: 13.82, 95% confidence interval: 1.59-119.51, p=0.017). Furthermore, a tumor size greater than 2 cm was also significantly associated with an increased likelihood of ALNM (adjusted odds ratio: 2.14, 95% confidence interval: 1.16-3.93, p=0.014), as detailed in Table 3.

Table 2 Univariate analyses

Variable	All (n=200)	Non-ALNM (n=98)	ALNM (n=102)	χ^2	df	p-value
Age (years)				0.152	1	0.697
≤50	69	32 (46.4%)	37 (53.6%)			
>50	131	66 (50.4%)	65 (49.6%)			
Tumor size (mm)				6.629	1	0.010
≤20	71	44 (62.0%)	27 (38.0%)			
>20	129	54 (41.9%)	75 (58.1%)			
Tumor-to-skin distance (mm)				0.379	2	0.827
≤5	114	58 (50.9%)	56 (49.1%)			
5.1-10	75	35 (46.7%)	40 (53.3%)			
10.1-15	11	5 (45.5%)	6 (54.5%)			
Tumor location	200	98 (49.0%)	102 (51.0%)	9.766	3	0.021
Medial	39	23 (59.0%)	16 (41.0%)			
Lateral	127	62 (48.8%)	65 (51.2%)			
Overlapping	22	12 (54.5%)	10 (45.5%)			
Subareolar	12	1 (8.3%)	11 (91.7%)			
Tumor grading	190	92 (48.4%)	98 (51.6%)	3.833	2	0.147
1	10	6 (60.0%)	4 (40.0%)			
2	109	58 (53.2%)	51 (46.8%)			
3	71	28 (39.4%)	43 (60.6%)			

Table 2 Continued

Variable	All (n=200)	Non-ALNM (n=98)	ALNM (n=102)	χ^2	df	*p*-value
ER	191	94 (49.2%)	97 (50.8%)	0.028	1	0.867
Negative	59	28 (47.5%)	31 (52.5%)			
Positive	132	66 (50.0%)	66 (50.0%)			
PR	191	94 (49.2%)	97 (50.8%)	0.120	1	0.729
Negative	88	45 (51.1%)	43 (48.9%)			
Positive	103	49 (47.6%)	54 (52.4%)			
HER2	191	94 (49.2%)	97 (50.8%)	3.498	2	0.174
Negative	97	53 (54.6)	44 (45.4%)			
Positive	45	17 (37.8%)	28 (62.2%)			
Equivocal	49	24 (49.0%)	25 (51.0%)			

Table 3 Bivariate and multivariate logistic regression analyses

Variable	Non-ALNM (n=98)	ALNM (n=102)	Bivariate analysis		Multivariate logistic regression analysis	
			Odds ratio (95% CI of OR)	*p*-value	Odds ratio (95% CI of OR)	*p*-value
Tumor size (mm)						
≤20	44 (62.0)	27 (38.0)	1		1	
>20	54 (41.9)	75 (58.1)	2.26 (1.25-4.09)	0.010	2.14 (1.16-3.93)	0.014
Tumor location						
Medial	23 (59.0%)	16 (41.0%)	1		1	
Lateral	62 (48.8%)	65 (51.2%)	1.50 (0.72-3.11)	0.354	1.48 (0.70-3.10)	0.297
Overlapping	12 (54.5%)	10 (45.5%)	1.19 (0.41-3.43)	0.947	1.08 (0.37-3.17)	0.882
Subareolar	1 (8.3%)	11 (91.7%)	15.81 (1.85-134.96)	0.006	13.82 (1.59-119.51)	0.017

Discussion

The tumor's location is significantly associated with the likelihood of ALNM, with tumors situated in the subareolar region demonstrating a higher probability of metastasis. These findings are consistent with studies by Manjer J et al. (2004)[21], Yoshihara E et al. (2012)[22], and Zhang Y et al. (2019)[23]. This could be explained by the breast's lymphatic drainage system, where deeper breast tissues drain through the mammary ducts. The lymphatic vessels in the breast converge into a main lymphatic duct beneath the subareolar region, forming a network known as Sappey's plexus.

This study found that tumors in the medial location had a lower frequency of metastasis to the axillary lymph nodes, similar to the findings of Yoshihara[22]. However, the medial position is associated with a poor

survival outcome, which may be due to the underestimation of the risk of internal mammary lymph node metastases[24].

Tumor-to-skin distance did not demonstrate a significant association with ALNM, which contrasts with findings from other studies. This may be explained by the relatively small average distance observed in our study (4.95 mm), with a maximum of 14.8 mm. In comparison, a study by Cunningham JE et al. (2006)[25] in the United States reported an average distance of 9.2 mm (maximum 23 mm). Similarly, Ansari B et al. (2011)[26], also based in the U.S., found an average distance of 9.1 mm (maximum 28 mm). A study by Sivakanthan T et al. (2024)[27] in the U.K. reported a median distance of 10 mm for patients with lymph node involvement and 12.5 mm for those without. Moreover, Essa MS et al. (2021)[20] in Egypt found an average distance of 14.6 mm. These variations in studies from the U.S., U.K., and Egypt indicate greater average tumor-to-skin distances compared to our findings. This discrepancy may be attributed to differences in breast size among women from different regions, which could influence the relationship between tumor-to-skin distance and ALNM. However, a study conducted by Eom YH et al. (2015)[28] in South Korea reported an average distance of 4.3 mm for patients without lymph node involvement and 4.67 mm for those with metastasis, which is closer to the findings in our study. Eom YH et al. had a sample size of 891 and found a statistically significant relationship at the level of 0.047, whereas this study included only 200 patients. The smaller sample size in our study may account for the absence of a significant association observed here. Furthermore, in our study, two patients had tumors located more than 14 mm from the skin, one of whom exhibited ALNM. This finding contrasts with that of Cunningham JE et al.[25], who reported no evidence of ALNM in 26 patients with tumors located more than 14 mm from the skin.

This study is the first in Thailand to examine the relationship between tumor-to-skin distance and ALNM, and its findings do not align with those of previous international studies. Consequently, tumor-to-skin distance cannot yet be regarded as a reliable predictive factor for ALNM. This may be due to variations in breast size, breast density, ultrasound probe pressure during examinations, and differences in the studied populations and demographic diversity across countries. Further prospective, multi-institutional, and international studies are recommended to validate these findings and explore additional contributing factors.

The results demonstrate a significant association between tumor size and ALNM. Larger tumors tend to have a higher likelihood of ALNM, corroborating the findings of previous studies[29-32]. This well-established correlation suggests that tumor size remains an important factor in predicting the risk of ALNM in breast cancer.

Those findings can be integrated with other prognostic factors to predict the progression of breast cancer. They will aid healthcare professionals in planning treatment

strategies, including axillary lymph node surgery, to maximize patient outcomes. Moreover, this information could help doctors communicate effectively with patients and mentally prepare them for surgery. Additionally, it holds potential for the development of risk prediction tools that can minimize unnecessary procedures and complications from axillary interventions.

Several limitations of this study should be acknowledged, as it was a retrospective review of existing data. Our methodology lacked standardization in consistently measuring minimal proximity, and we were unable to control the pressure applied by the ultrasound probe during the examination. This technical variable may have influenced the accuracy of tumor-to-skin distance measurements. Additionally, some lesions exhibited poorly defined borders, while others had hyperechoic halos surrounding them. Finally, breast size was not considered, despite the potential impact of tumor size relative to breast size on proximity to the skin, particularly in smaller breasts.

This study propose conducting a prospective multicenter study with a standardized protocol for ultrasonography measurements, comparing these with other imaging modalities, such as MRI or mammography, and actual pathological measurements. Additionally, variables such as breast size, clinical staging, histologic type, molecular subtype, and lymphovascular invasion should be systematically collected to ensure comprehensive data for the development of a predictive model.

Conclusions

Preoperative ultrasonographic tumor location has the potential to serve as a prognostic indicator for ALNM. Tumors located in the subareolar region are significantly more likely to be associated with ALNM compared to those in other breast regions. This finding emphasizes the relevance of tumor location as a factor in risk assessment and can contribute to the optimization of treatment strategies when used alongside other prognostic indicators.

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