

# Distance between tumor and nipple as a prognostic factor in breast cancers

## Opposite effects in young and old patients

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### Abstract

The present study aimed to investigate the prognostic implication of distance from tumor to nipple according to clinicopathological factors with known prognostic value.

We retrospectively identified 961 patients of invasive breast cancer from January 2000 to April 2016. Clinicopathological information was extracted from hospital database and distance from tumor to nipple was objectively measured during surgeries. Overall survival (OS) and disease-free survival (DFS) were compared among patients with tumor-nipple distance  $\leq 2$ , 2 to 5, and  $> 5$  cm. Subgroup analyses were performed according to age at diagnosis ( $\leq 35$  vs  $> 35$ ), tumor size, histological features, treatment, axillary nodal metastasis and lymphovascular invasion.

A total of 627 cases were included in statistical analysis. There was no difference detected in OS or DFS among patients with different tumor-nipple distance. Better OS was associated with greater tumor-nipple distance in old patients (HR=0.582, 95%CI: 0.345–0.982,  $P=0.042$ ), while the association between OS and tumor-nipple distance was not observed in young patients. DFS was influenced by tumor-nipple distance in both young (HR=5.321, 95%CI: 1.151–24.595,  $P=0.032$ ) and old (HR=0.593, 95%CI: 0.385–0.913,  $P=0.018$ ) patients with opposite effects.

Tumor-nipple distance can be adopted as a prognostic factor of breast cancer and it functions oppositely in young and old patients. Multicenter prospective studies with larger sample size are needed to validate the result.

**Abbreviations:** DFS = disease-free survival, ER = estrogen receptor, Her2 = human epidermal growth factor receptor 2, OS = overall survival, PR = progesterone receptor.

**Keywords:** breast cancer, survival, tumor-nipple distance

## 1. Introduction

In breast cancers, the distance from tumor to nipple seems a factor easily neglected but has been found associated with axillary lymph node metastasis in several studies.<sup>[1–5]</sup> In terms of the anatomy of lymphatic drainage of the breast, the superficial

drainage was richly scattered from the skin to a 3 mm depth. The axillary or lateral pathway of breast lymphatic drainage is fed by Sappey's Plexus,<sup>[6]</sup> ducts satellite lymphatics and parenchymal lymphatics, interacting with internal mammary and retromammary pathway,<sup>[7]</sup> indicating that the possibility of axillary node metastasize via the lymphatics might be related to the location of tumor.<sup>[8]</sup> With axillary lymph node status being an idea independent prognostic factor, the tumor-nipple distance revealed potential prognostic significance.<sup>[9,10]</sup> Up to now, few studies has addressed the issue. In 2001, a retrospective study claimed that mammographic nipple to lesion distance of  $< 40$  mm was a factors to increase the likelihood of recurrence in ductal carcinoma of the breast.<sup>[11]</sup> However, in 2015, a study reported null significant correlation between breast cancer distance from the skin  $< 3$  mm and ipsilateral breast cancer recurrence or recurrence-free survival in breast cancers.<sup>[3]</sup>

The present study aimed to investigate the prognostic implication of distance from tumor to nipple according to clinicopathological factors with known prognostic value, aiming to unearth the prognostic potential of tumor-nipple distance in each certain circumstance.

## 2. Materials and methods

### 2.1. Patient selection and data extraction

We retrospectively identified from hospital database 961 patients, who were pathologically diagnosed with invasive breast cancer and treated at West China Hospital of Sichuan University between January 2000 and April 2016. Each patient materials

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were screened and those who had recorded distance from tumor to nipple were included. Accordingly, the following exclusion criteria were applied: (1) male patients, (2) bilateral breast cancers, (3) multifocal or multicentric tumors, (4) recurrent cancer or prior history of breast cancer, (5) metastasis at diagnosis, (6) Paget's disease. The study was exempt from informed consent because it only included retrospective analysis of anonymous data. This study was approved by the West China Hospital Research Ethics Committee.

The clinicopathological data collected for each patient included: distance from tumor to nipple, date of birth, age at diagnosis, pathological tumor size and clinical stage, tumor histology, tumor grade, presence of lymphovascular invasion, axillary nodal status, status of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (Her2) gene amplification. We stratified the tumor-nipple distance into 3 groups: <2, 2 to 5, and >5 cm. ER and PR were considered positive if the number of nuclear staining was in at least 1% of the tumor cells. Percentages of ki-67 expression were recorded. In dichotomous analyses, high Ki-67 expression was defined as immunostaining in more than 14% tumor cells. Her2 were regarded as negative at 0 (no immunostaining) or 1+ (immunostaining in  $\leq 10\%$  of tumor cells); uncertain at 2+ (weak or incomplete membrane immunostaining in  $>10\%$  of tumor cells and complete membrane immunostaining in  $\leq 10\%$  of tumor cells); 3+ (strong complete membrane immunostaining in  $>10\%$  of tumor cells) or Her2 overexpression confirmed by fluorescence in situ hybridisation (FISH) as positive. Molecular subtypes were defined by ER, PR, Her2 status and ki-67 expression.<sup>[12]</sup>

## 2.2. Survival analysis and statistical analysis

We evaluated the association of distance from tumor to nipple with overall survival (OS) and disease-free survival (DFS) among all the included cases and in each subtype. OS was defined as the period from the date of breast cancer diagnosis until the date of death from any cause or the date of last follow-up. DFS was defined as the period from the date of breast cancer diagnosis until the date of recurrence, metastasis, death or the date of last follow-up. Subgroups were adopted based on age at diagnosis ( $\leq 35$  vs  $>35$ ), tumor size, clinical stage, WHO classification, ER, PR, Her2 status, ki-67 expression, molecular subtype, treatment (radiotherapy, chemotherapy, neoadjuvant chemotherapy and endocrine therapy), axillary nodal metastasis and lymphovascular invasion.

Survival curves were obtained using the Kaplan-Meier method, and were compared using the log-rank test. Comparisons of clinical and pathologic features among patients were performed with one-way analysis of variance, Pearson's Chi-square test or Fisher's exact test. Univariate and multivariate analyses were conducted using Cox proportional hazards model. For each factor analyzed, hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated, and covariates with  $P$  value  $<0.05$  under univariate analyses were selected in multivariate analyses to build the model. The log-rank test was used to compare survival distributions and the survival distributions survival curves were drawn with Kaplan-Meier method. All tests were two-tailed and a  $P$  value  $<0.05$  was considered significant. The statistical analysis was performed using SPSS software 16.0 for Windows (SPSS Inc., Chicago, IL, USA).

## 3. Result

### 3.1. Clinicopathological characteristics

Among 961 patients with breast cancer from January 2000 to April 2016, 84 cases were excluded for the following reasons: male patients ( $n=6$ ), bilateral breast cancers ( $n=20$ ), multifocal or multicentric tumors ( $n=29$ ), recurrence at diagnosis ( $n=6$ ), prior history of breast surgery ( $n=11$ ), metastasis at diagnosis ( $n=8$ ), Paget's disease ( $n=2$ ), tumor fixed to chest wall ( $n=2$ ). In the 877 cases left, 627 cases had precisely recorded data of distance from tumor to nipple, thus were included in statistical analysis.

Clinicopathological features for the included cases and comparisons of the patients among patients with different tumor-nipple distances were summarized in Table 1.

### 3.2. Overall and subgroup analyses of OS and DFS in patients with different tumor-nipple distance

The OS and DFS of patients with tumor-nipple distance  $<2$ , 2 to 5, and  $>5$  cm were compared. Subgroup based on age, tumor size, clinical stage, histological parameters, molecular subtype, therapy, axillary nodal involvement and lymphovascular invasion were also performed and HRs and CI95% were listed in Table 1. The OS and DFS of patients with different categories of tumor-nipple distance among subgroups were summarized in Table 2. According to tumor-nipple distance in subgroup analysis by endocrine therapy, OS was significantly associated with tumor-nipple distance in patients who received endocrine therapy (HR=0.404, 95%CI: 0.176–0.926,  $P=0.032$ ). DFS was significantly associated with tumor-nipple distance in patients without axillary nodal metastasis (HR=0.449, 95%CI: 0.202–0.999,  $P=0.0498$ ). There was no difference detected in OS or DFS among patients with different tumor-nipple distance (Fig. 1). However, when we arbitrarily define patients aged  $\leq 35$  years old as young patients and those  $>35$  as old patients when performing age based subgroup analysis, OS was significantly associated with tumor-nipple distance in old patients (HR=0.582, 95%CI: 0.345–0.982,  $P=0.042$ ), while DFS was influenced by tumor-nipple distance in both young (HR=5.321, 95%CI: 1.151–24.595,  $P=0.032$ ) and old (HR=0.593, 95%CI: 0.385–0.913,  $P=0.018$ ) patients with opposite effects (Fig. 2). In patients with breast cancer aged  $<35$  years old, greater tumor-nipple distance end up in worse DFS. While in patients older than 35 years old, the greater the tumor-nipple distance was, the better the outcomes. We performed tumor-nipple-distance-based subgroup analysis, OS was significantly related to tumor size in patients whose tumor-nipple distance more than 5 cm (HR=4.378, 95%CI: 1.627–11.779,  $P=0.003$ ). So does the DFS (HR=6.69, 95%CI: 2.986–14.987,  $P<0.001$ ) (Fig. 3).

### 3.3. Univariate and multivariate analysis of prognostic factors

The result of univariate and multivariate analysis with OS and DFS are shown in Table 3. Age at diagnosis, clinical stage and lymphovascular invasion contributes to OS significantly, while endocrine therapy had a significant beneficial effect on DFS apart from similar adverse effects from age at diagnosis, clinical stage and lymphovascular invasion.

**Table 1**  
**Patients and tumor characteristics upon the distance from breast cancer to nipple.**

Characteristics	Overall (n=627)	≤2cm (n=252)	2cm~5 cm (n=311)	>5 cm (n=64)	P value
Age (mean±SD)	48.1±10.3	47.9±10.5	48.2±10.2	48.1±10.0	.957
Tumor size, cm (mean±SD)	2.8±1.5	3.1±1.8	2.7±1.3	2.5±0.8	.006
Follow-up duration, month (mean±SD)	54±44.6	56.1±44.6	51.3±43.7	58.5±48.8	.309
Clinical stage					.012
I	100 (17.5%)	32 (13.7%)	53 (19.0%)	15 (24.6%)	
II	305 (53.2%)	116 (49.8%)	154 (55.2%)	35 (57.4%)	
III	168 (29.3%)	85 (36.5%)	72 (25.8%)	11 (18.0%)	
WHO classification					.414
Grade 1	11 (2.5%)	4 (2.3%)	6 (2.7%)	1 (2.0%)	
Grade 2	148 (33.2%)	62 (35.8%)	75 (33.8%)	11 (21.6%)	
Grade 3	287 (64.3%)	107 (61.8%)	141 (63.5%)	39 (76.5%)	
ER					.046
Negative	206 (33.3%)	74 (29.6%)	103 (33.7%)	29 (46.0%)	
Positive	413 (66.7%)	176 (70.4%)	203 (66.3%)	34 (54.0%)	
PR					.926
Negative	215 (34.7%)	85 (34.0%)	107 (35.0%)	23 (36.5%)	
Positive	404 (65.3%)	165 (66.0%)	199 (65.0%)	40 (63.5%)	
Her2 status					.194
Negative	449 (73.4%)	173 (70.3%)	229 (75.3%)	47 (75.8%)	
Positive	104 (17.0%)	50 (20.3%)	48 (15.8%)	6 (9.7%)	
Uncertain	59 (9.6%)	23 (9.3%)	27 (8.9%)	9 (14.5%)	
Ki-67 expression, % (mean±SD)	32.5±22.4	31.6±20.6	32.3±22.6	37.4±26.8	.201
High expression	418 (75.7%)	166 (77.2%)	208 (74.8%)	44 (74.6%)	.809
Low expression	134 (24.3%)	49 (22.8%)	70 (25.2%)	15 (25.4%)	
Molecular subtype					.370
Luminal A	102 (18.6%)	35 (16.1%)	55 (20.0%)	12 (21.8%)	
Luminal B	300 (54.8%)	127 (58.5%)	142 (51.6%)	31 (56.4%)	
Triple negative	107 (19.6%)	36 (16.6%)	61 (22.2%)	10 (18.2%)	
Her2-enriched	38 (6.9%)	19 (8.8%)	17 (6.2%)	2 (3.6%)	
Radiotherapy					.394
Yes	242 (38.7%)	90 (35.7%)	128 (41.3%)	24 (37.5%)	
No	384 (61.3%)	162 (64.3%)	182 (58.7%)	40 (62.5%)	
Chemotherapy					.362
Yes	600 (95.8%)	245 (97.2%)	294 (94.8%)	61 (95.3%)	
No	26 (4.2%)	7 (2.8%)	16 (5.2%)	3 (4.7%)	
Neoadjuvant chemotherapy					.002
Yes	87 (13.9%)	46 (18.3%)	40 (12.9%)	1 (1.6%)	
No	539 (86.1%)	206 (81.7%)	270 (87.1%)	63 (98.4%)	
Endocrine therapy					.686
Yes	404 (64.5%)	166 (65.9%)	195 (62.9%)	43 (67.2%)	
No	222 (35.5%)	86 (34.1%)	115 (37.1%)	21 (32.8%)	
Axillary nodal metastasis					.063
Yes	319 (51.2%)	140 (56.0%)	153 (49.5%)	26 (40.6%)	
No	304 (48.8%)	110 (44.0%)	156 (50.5%)	38 (59.4%)	
Lymphovascular invasion					.684
Yes	17 (2.7%)	6 (2.4%)	10 (3.3%)	1 (1.6%)	
No	603 (97.3)	244 (97.6%)	296 (96.7%)	63 (98.4%)	

ER=estrogen receptor, Her2=human epidermal growth factor receptor 2, PR=progesterone receptor.

#### 4. Discussion

The present study aimed to investigate the prognostic implication of distance from tumor to nipple according to clinicopathological factors with known prognostic value, aiming to unearth the prognostic potential of tumor-nipple distance in each certain circumstance. Our study included a total of 627 breast cancer cases with the average follow-up of 54±44.6 months and we found that the distance between tumor and nipple was a significant prognostic factor in breast cancers and functions oppositely in young and old patients.

In the previous studies on the relationships between tumor proximity and axillary lymph node involvement as well as breast

cancer outcomes, the distance between tumor and nipple were all measured through imaging modalities such as mammography,<sup>[1]</sup> ultrasound<sup>[3-5,13]</sup> and MRI.<sup>[2]</sup> However, when ultrasound was performed, the pressure given by the probe might result in a smaller distance compared with actual scenario. Specially, the pressure from the probe varies among film readers. In certain studies, adjustments were mandatory to reduce the reader associated bias. These subjective differences hamper the precision and reproducibility. For mammography, the fluorescence figure could only reveal distance on either mediolateral oblique (MLO) or craniocaudal (CC) views, which obviously do not depict the whole picture of the three-dimensional structure of the breasts. As for MRI, similar limitation

**Table 2****Overall survival and disease-free survival of three categories of tumor-nipple distance among subgroups.**

Subgroup	OS		DFS	
	HR (95%CI)	P value	HR (95%CI)	P value
Overall	0.682 (0.418, 1.113)	.126	0.694 (0.464, 1.040)	.077
Age				
≤35	5.442 (0.824, 35.939)	.079	5.321 (1.151, 24.595)	<b>.032</b>
>35	0.582 (0.345, 0.982)	<b>.042</b>	0.593 (0.385, 0.913)	<b>.018</b>
Tumor size				
T1	0.541 (0.201, 1.453)	.223	0.522 (0.227, 1.203)	.127
T2–T4	1.004 (0.508, 1.985)	.990	0.872 (0.493, 1.542)	.637
Clinical stage				
I	0.690 (0.120, 3.954)	.677	0.458 (0.090, 2.336)	.347
II	0.508 (0.162, 1.592)	.245	0.450 (0.193, 1.052)	.065
III	0.828 (0.443, 1.547)	.554	1.051 (0.634, 1.741)	.847
WHO classification				
Grade 1*	–	–	–	–
Grade 2	0.245 (0.031, 1.905)	.179	0.968 (0.423, 2.218)	.939
Grade 3	0.739 (0.398, 1.370)	.336	0.616 (0.344, 1.105)	.104
ER				
Negative	0.745 (0.381, 1.456)	.390	0.781 (0.435, 1.402)	.407
Positive	0.568 (0.264, 1.220)	.147	0.622 (0.347, 1.114)	.111
PR				
Negative	0.771 (0.408, 1.459)	.424	0.787 (0.449, 1.379)	.402
Positive	0.557 (0.238, 1.304)	.178	0.619 (0.335, 1.146)	.127
Her2 status				
Negative	0.657 (0.370, 1.169)	.153	0.627 (0.383, 1.026)	.063
Positive	1.362 (0.398, 4.659)	.623	1.165 (0.436, 3.115)	.760
Uncertain	0.521 (0.056, 4.864)	.567	0.699 (0.173, 2.822)	.615
Ki-67 expression				
High	0.840 (0.474, 1.487)	.549	0.634 (0.371, 1.083)	.095
Low	0.229 (0.051, 1.022)	.053	0.674 (0.291, 1.560)	.356
Molecular subtype				
Luminal A	0.254 (0.055, 1.165)	.078	0.601 (0.226, 1.602)	.309
Luminal B	0.843 (0.393, 1.806)	.660	0.662 (0.325, 1.349)	.256
Triple negative	0.921 (0.372, 2.277)	.858	0.646 (0.277, 1.507)	.312
Her2-enriched	1.871 (0.112, 31.363)	.663	2.884 (0.560, 14.867)	.206
Radiotherapy				
Yes	0.556 (0.282, 1.100)	.092	0.691 (0.398, 1.197)	.187
No	0.828 (0.407, 1.682)	.601	0.676 (0.369, 1.241)	.207
Chemotherapy				
Yes	0.691 (0.423, 1.237)	.138	0.699 (0.467, 1.046)	.082
No*	–	–	–	–
Neoadjuvant chemotherapy				
Yes	0.721 (0.142, 3.662)	.694	0.491 (0.104, 2.330)	.371
No	0.688 (0.409, 1.157)	.158	0.713 (0.467, 1.089)	.117
Endocrine therapy				
Yes	0.404 (0.176, 0.926)	<b>.032</b>	0.588 (0.325, 1.065)	.080
No	0.974 (0.522, 1.817)	.934	0.811 (0.464, 1.419)	.464
Axillary nodal metastasis				
Yes	0.797 (0.449, 1.414)	.437	0.916 (0.569, 1.476)	.718
No	0.584 (0.223, 1.528)	.273	0.449 (0.202, 0.999)	<b>.0498</b>
Lymphovascular invasion				
Yes	1.343 (0.251, 7.179)	.730	0.867 (0.234, 3.219)	.832
No	0.622 (0.367, 1.056)	.079	0.612 (0.360, 1.040)	.070

DFS=disease-free survival, ER=estrogen receptor, Her2=human epidermal growth factor receptor 2, OS=overall survival, PR=progesterone receptor.

\* Cox Regression could not continue due to lack of endpoint event in the subgroups.

as well as patients' position (prone) related biases exist. At our institution, it is the standard routine protocol to measure and record the distance from tumor to nipple during surgery. The distance was recorded in centimeters and was measured radially from nipple to the epicenter rather than the edge of tumor, thus to obviate confounders resulting from variable tumor size. These data were prospectively archived and retrospectively retrieved.

Overall analyses indicated null prognostic value of tumor proximity to nipple. This result was not in consistence with conclusions that axillary lymph node metastasis was associated with a smaller distance from tumor to nipple.<sup>[3–5]</sup> While more recently, a retrospective study with 266 patients revealed null difference in pathological N stages between MRI-based group of short tumor-nipple distance (<2.0 cm) and group of long tumor-

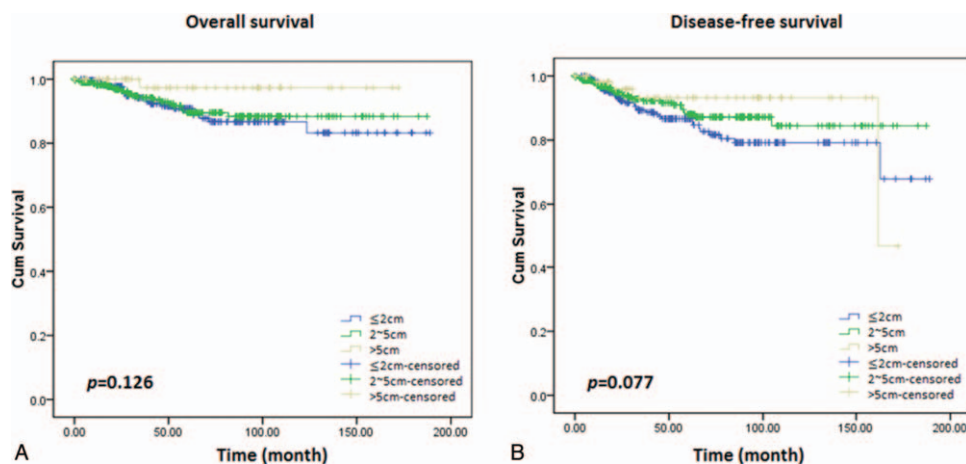


Figure 1. Kaplan-Meier analysis of survival outcomes according to tumor-nipple distance in all patients. (A) Overall survival and (B) disease-free survival.

nipple distance ( $\geq 2.0$ cm).<sup>[2]</sup> Canello et al found younger patients (age > 35) had a higher risk of relapse, independent of their breast cancer subtype.<sup>[14]</sup> When we stratified the patients according to age at diagnosis, an astonishing phenomenon was that OS was significantly associated with tumor-nipple distance in old patients, while DFS was influenced by tumor-nipple

distance in both young and old patients with opposite effects. To be specific, in patients with breast cancer aged < 35 years old, greater tumor-nipple distance end up in worse outcomes. While in patients older than 35 years old, the greater the tumor-nipple distance was, the better the outcomes. One possibility is young patients concentrate more on appearance and would like to take

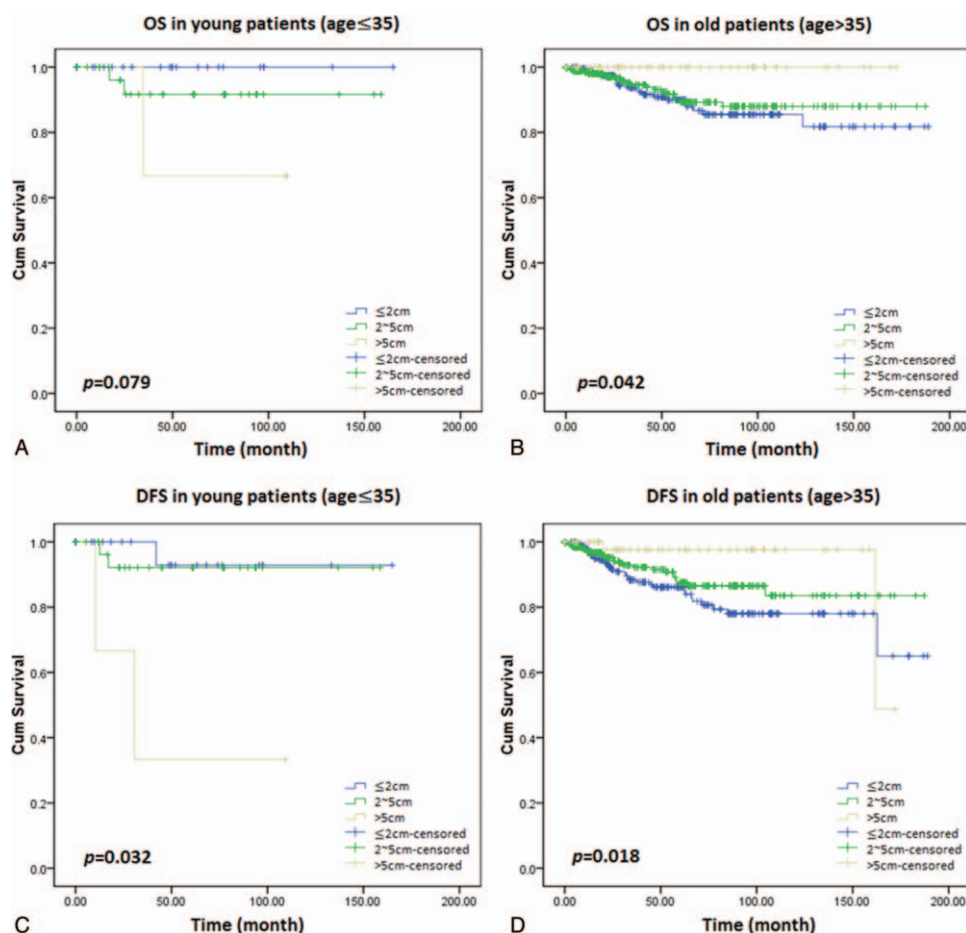
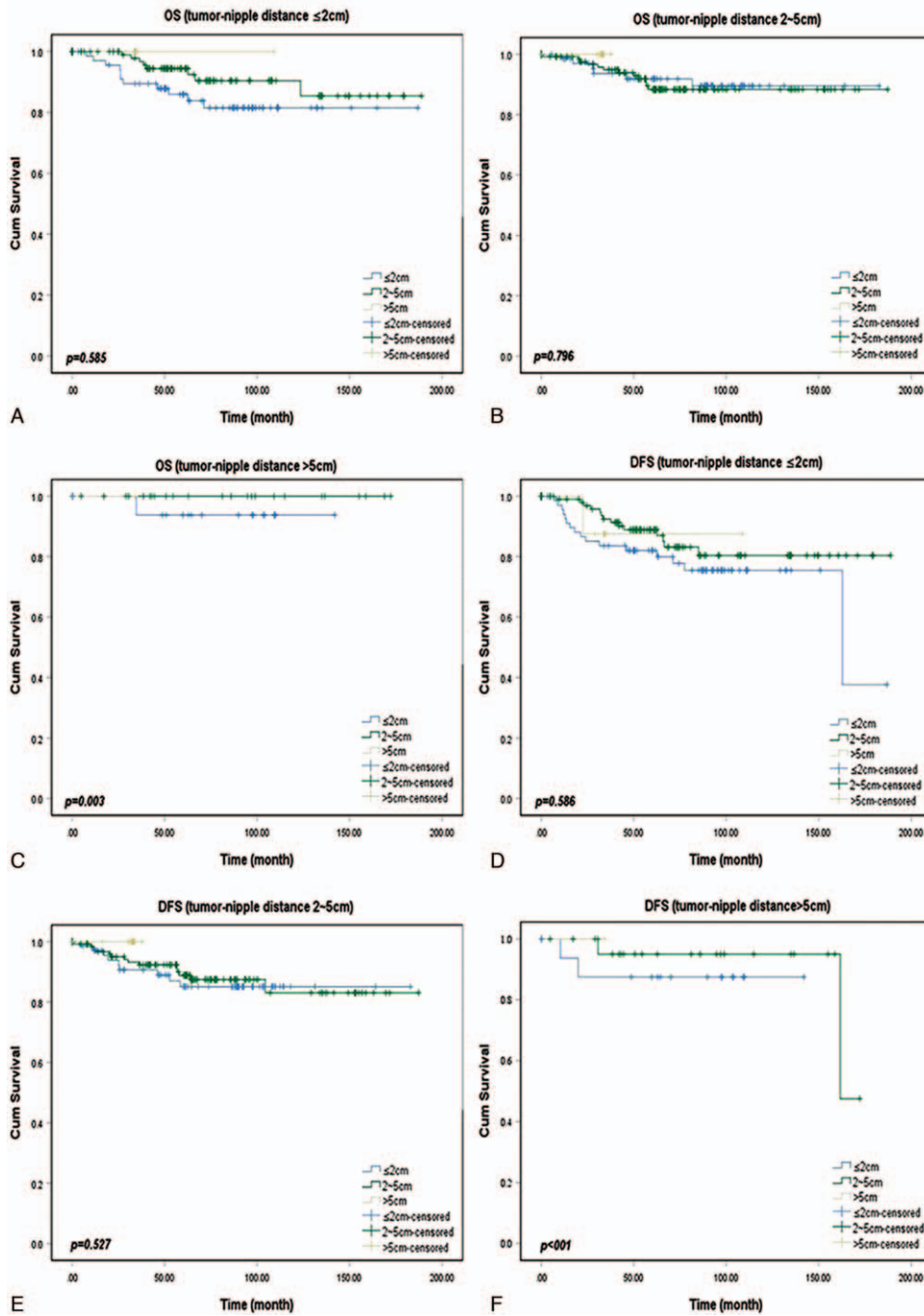


Figure 2. Kaplan-Meier analysis of survival outcomes according to tumor-nipple distance in subgroup analysis by age. (A) Overall survival of young patients (age ≤ 35), (B) overall survival of old patients (age > 35), (C) disease-free survival of young patients (age ≤ 35), and (D) disease-free survival of old patients (age > 35).



**Figure 3.** Kaplan-Meier analysis of survival outcomes according to tumor size in subgroup analysis by tumor-nipple distance. (A) Overall survival of patients whose tumor-nipple distance <2 cm, (B) overall survival of patients whose tumor-nipple distance 2–5 cm, (C) overall survival of patients whose tumor-nipple distance more than 5 cm, (D) disease-free survival of patients whose tumor-nipple distance <2 cm, (E) disease-free survival of patients whose tumor-nipple distance 2–5 cm, and (F) disease-free survival of patients whose tumor-nipple distance more than 5 cm.

breast conserving surgery. Among 627 patients, 22.81% of young patients (age > 35) take breast conserving surgery, while 9.1% of old patients (age > 35) take the same surgery. Radiotherapy after surgery gradually popularized around 2011.<sup>[15]</sup> 23.1% of included young patients who take breast conserving surgery did not receive radiotherapy which means that part of younger patients not receiving adequate treatment intensity. With regard to other possible explanations, we

postulate it may be related to lymphatic drainage system of the breast. Still, anatomical research and experiments are needed to enlighten the mechanism about what happened to the breast cancer patients during their 35 or around. When we stratified the patients according to tumor-nipple distance at diagnosis, OS was significantly related to tumor size in patients whose tumor-nipple distance more than 5 cm, while DFS was influenced by tumor size in the same group. But only 22 patients had tumors larger than 5

**Table 3**  
**Univariate and multivariate analysis for overall survival and disease-free survival.**

Covariate	OS				DFS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Age at diagnosis	1.047 (1.020, 1.076)	.001	1.046 (1.013, 1.080)	.006	1.026 (1.003, 1.049)	.027	1.030 (1.005, 1.055)	.017
Tumor size	1.384 (1.207, 1.587)	<.001	1.366 (0.933, 2.000)	.109	1.260 (0.997, 1.592)	.053		
Clinical stage	3.703 (2.077, 6.602)	<.001	2.971 (1.306, 6.759)	.009	3.384 (2.142, 5.346)	<.001	2.946 (1.675, 5.182)	<.001
WHO classification	2.740 (1.085, 6.916)	.033	1.623 (0.604, 4.357)	.337	1.448 (0.777, 2.696)	.244		
ER	0.515 (0.279, 0.950)	.034	0.745 (0.219, 2.537)	.638	0.680 (0.408, 1.133)	.139		
PR	0.350 (0.187, 0.655)	.001	0.733 (0.247, 2.179)	.577	0.501 (0.303, 0.829)	.007	1.070 (0.557, 2.056)	.839
Her2 status	0.938 (0.803, 1.095)	.417			0.995 (0.899, 1.100)	.915		
Ki-67 expression	1.001 (0.986, 1.015)	.918			0.999 (0.987, 1.012)	.887		
Molecular subtype	1.161 (0.790, 1.706)	.449			1.136 (0.814, 1.586)	.454		
Radiotherapy	1.492 (0.816, 2.727)	.193			1.480 (0.899, 2.435)	.123		
Chemotherapy	21.146 (0.010, 43319.835)	.433			22.284 (0.068, 7343.846)	.294		
Neoadjuvant chemotherapy	1.311 (0.551, 3.116)	.540			1.103 (0.524, 2.321)	.796		
Endocrine therapy	0.344 (0.189, 0.626)	<.001	0.878 (0.274, 2.814)	.827	0.409 (0.250, 0.671)	<.001	0.441 (0.230, 0.845)	.014
Axillary nodal metastasis	2.881 (1.452, 5.717)	.002	1.081 (0.361, 3.238)	.889	2.483 (1.437, 4.290)	.001	1.062 (0.524, 2.154)	.867
Lymphovascular invasion	5.847 (2.295, 14.896)	<.001	7.890 (2.540, 24.510)	<.001	5.294 (2.274, 12.325)	<.001	4.409 (1.835, 10.590)	.001
Distance from tumor to nipple	0.682 (0.418, 1.113)	.126			0.694 (0.464, 1.040)	.077		

DFS=disease-free survival, ER=estrogen receptor, Her2=human epidermal growth factor receptor 2, OS=overall survival, PR=progesterone receptor.

cm. A possible reason that low number of included patients with tumor larger than 5 cm is that they were more likely to receive neoadjuvant chemotherapy before surgery, or even to lose opportunity for surgery. So, we did not include them.

Limitations of the present study needs to be mentioned. First, tumor size relative to breast size may affect proximity to the skin, particularly in smaller breasts. When ideally, the ratio of distance to breast size should also be analyzed. However, the size of breast was not taken into account due to lack of data. Nonetheless, the breast sizes of Asian women are generally smaller and less variable compared to Western women, making the potential imperfection less powerful. Moreover, we evaluated the distance from the center rather than the edge of tumor to nipple, which also weakened the affect from breast size. In addition, we excluded male patients because male breast cancers are more likely to be beneath nipple-areola complexes and contributes to the biases. Second, there was considerable missing data, decreasing the sample size significantly. Besides, the pathological information of some included cases was missing. For example, Her2 were regarded as uncertain at 2+ but did not get FISH confirmation in 59 patients, thus were not able to be included in subgroup analyses by molecular subtype.

In conclusion, the present study found that proximity to nipple a significant prognostic factor in breast cancers and functions oppositely in young and old patients. However, multicenter studies with larger sample size are needed to confirm the conclusion and anatomical studies are desired to elaboration the exact structure as well as the mechanism.

**Author contributions**

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