Factors associated with lymph node metastasis and its prognostic impact in breast cancer patients with small tumors (≤2cm)

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Introduction

Although previous randomized controlled trials have suggested that axillary surgery may be omitted in patients with clinically node-negative breast cancer with tumor ≤ 2cm (pT1), approximately 15% of these patients were found to have lymph node (LN) metastasis. Furthermore, while these studies demonstrated that axillary surgery, including sentinel LN biopsy, does not provide a therapeutic benefit, concern remain regarding the prognostic impact of occult LN metastasis. Therefore, the aim of our study was to identify factors associated with LN metastasis in small tumors (≤ 2cm) and to analyzed its impact on recurrence.

Methods

We identified patients with pT1 primary breast cancer who underwent treatment at two hospitals between September 2003 and December 2019. To ensure accurate assessment of pathologic LN metastasis, patients who received neoadjuvant systemic therapy or did not undergo axillary surgery were excluded. Multivariate analysis was performed to identify factors associated with LN metastasis and to evaluate the impact of LN metastasis on recurrence-free survival (RFS).

Results

A total of 1,745 patients were included in the study, of whom 384 (22.0%) had axillary LN metastasis. In the multivariate binary logistic regression model, LN metastasis was significantly more common in tumors larger than 1cm (odds ratio [OR], 2.94; 95% confidence intervals [CI], 0.15-4.08; P<0.001) and in the presence of lympho-vascular invasion (OR, 4.41; 95% CI, 3.37-5.78; P<0.001) while it was less frequent in tumors with histology other than ductal or lobular type (OR, 0.45; 95% CI, 0.22-0.89; P=0.022). In the multivariate Cox proportional hazard model, LN metastasis was identified as a significant risk factor related with worse RFS (hazard ratio, 1.99; 95% CI, 1.26-3.14; P=0.003). In subgroup analysis, LN metastasis was associated with poor prognosis across most subgroups, with its impact being particularly pronounced in patients with tumors>1cm, histologic grade I or II, and the HR+/HER2- subtype.

Conclusion

Our study found the factors associated with a higher likelihood of LN metastasis in small (pT1) breast tumors and confirmed that LN metastasis is associated with worse prognosis. Because the presence of LN metastasis can increase the risk of recurrence, even in small tumors, careful consideration should be given to performing axillary surgery to avoid potential undertreatment in patients with a high risk of LN metastasis.

Table 1. Baseline characteristics of enrolled patients

	LN negative (N=1361), (%)	LN positive (N=384), (%)	All (N=1745), (%)	*P* value
Age (SD)	51.9 (10.6)	52.4 (10.7)	52.0 (10.6)	0.493
Menopausal status				0.095
Premenopausal	693 (50.9)	177 (46.1)	870 (49.9)	
Postmenopausal	668 (49.1)	207 (53.9)	875 (50.1)	
Tumor size (mm)				<0.001
≤10	515 (37.8)	52 (13.5)	567 (32.5)	
>10	846 (62.2)	332 (86.5)	1178 (67.5)	
Tumor histology				0.003
Ductal	1226 (90.1)	367 (95.6)	1593 (91.3)	
Lobular	41 (3.0)	7 (1.8)	48 (2.8)	
Others	94 (6.9)	10 (2.6)	104 (6.0)	
HG				0.002
I/II	1011 (74.3)	288 (75.0)	1299 (74.7)	
III	268 (19.7)	89 (23.2)	357 (20.5)	
Unknown	82 (6.0)	7 (1.8)	89 (5.1)	
NG				0.002
I/II	835 (61.4)	245 (63.8)	1080 (61.9)	
III	300 (22.0)	102 (26.6)	402 (23.0)	
Unknown	226 (16.6)	37 (9.6)	263 (15.1)	
LVI				<0.001
Negative	1142 (83.9)	210 (54.7)	1352 (77.5)	
Positive	164 (12.0)	160 (41.7)	324 (18.6)	
Unknown	55 (4.0)	14 (3.6)	69 (4.0)	
Subtype				0.325
HR+/HER2-	904 (66.4)	261 (68.0)	1165 (66.8)	
HER2+	288 (21.2)	88 (22.9)	376 (21.5)	
TNBC	156 (11.5)	33 (8.6)	189 (10.8)	
Unknown	13 (1.0)	2 (0.5)	15 (0.9)	
Ki-67 LI				0.713
<20%	680 (50.0)	183 (47.7)	863 (49.5)	
≥20%	579 (42.5)	172 (44.8)	751 (43.0)	
Unknown	102 (7.5)	29 (7.6)	131 (7.5)	

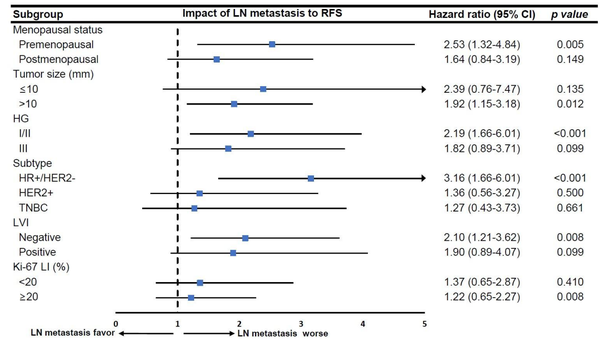
Table 2. Uni- and multivariate analysis of factor associated with LN metastasis

	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (SD)	1.00 (0.99-1.04)	0.493		
Menopausal status				
Premenopausal	Ref.			
Postmenopausal	1.21 (0.97-1.52)	0.095		
Tumor size (mm)				
≤10	Ref.		Ref.	
>10	3.89 (2.84-5.31)	<0.001	2.94 (0.12-4.08)	<0.001
Tumor histology				
Ductal	Ref.		Ref.	
Lobular	0.57 (0.25-1.28)	0.174	0.83 (0.36-1.91)	0.661
Others	0.36 (0.18-0.69)	0.002	0.45 (0.22-0.89)	0.022
HG				
I/II	Ref.			
III	1.17 (0.89-1.53)	0.271		
NG				
I/II	Ref.			
III	1.16 (0.89-1.51)	0.278		
LVI				
Negative	Ref.		Ref.	
Positive	5.31 (4.08-6.90)	<0.001	4.41 (3.37-5.78)	<0.001
Subtype				
HR+/HER2-	Ref.			
HER2+	1.06 (0.80-1.39)	0.687		
TNBC	0.73 (0.49-1.09)	0.127		
Ki-67 LI				
<20%	Ref.			
≥20%	1.10 (0.87-1.40)	0.412		

Table 3. Uni- and multivariate analysis of factor associated with RFS

	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
LN metastasis				
Negative	Ref.		Ref.	
Positive	2.27 (1.53-3.38)	<0.001	1.99 (1.26-3.14)	0.003
Menopausal status				
Premenopausal	Ref.			
Postmenopausal	1.19 (0.81-1.76)	0.375		
≤10	Ref.			
>10	1.29 (0.83-2.01)	0.251		
Tumor histology				
Ductal	Ref.			
Lobular	0.35 (0.48-2.48)	0.291		
Others	0.87 (0.38-1.99)	0.742		
HG				
I/II	Ref.		Ref.	
III	2.47 (1.65-3.71)	<0.001	1.72 (1.07-2.77)	0.026
LVI				
Negative	Ref.		Ref.	
Positive	1.96 (1.27-3.01)	0.002	1.37 (0.85-2.22)	0.197
Subtype				
HR+/HER2-	Ref.		Ref.	
HER2+	1.64 (1.03-2.62)	0.038	1.48 (0.89-2.46)	0.127
TNBC	2.56 (1.56-4.20)	<0.001	2.24 (1.25-4.02)	0.007
Ki-67 LI				
<20%	Ref.			
≥20%	1.40 (0.94-2.09)	0.102		
Chemotherapy				
Not performed	Ref.			
Performed	1.65 (0.97-2.82)	0.067		

Figure 1. Forest plot of subgroup analysis for the impact of LN metastasis on RFS



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