Original Article

Predictive clinicopathological characteristics affecting sentinel lymph node metastasis in early breast cancer patients

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Background: Sentinel lymph node biopsy (SLNB) is one of the standard procedures for breast cancer patients without clinically detected axillary lymph nodes. However, 60–78% of patients suffered from unnecessary invasive axilla surgery. Our objective is to investigate predictive clinicopathological factors affecting sentinel lymph node (SLN) status in early breast cancer patients.

Methods: There were 324 patients who were diagnosed as invasive breast cancer and took SLNB in Peking Union Medical College Hospital (PUMCH). They were categorized into the two groups according to axillary lymph node status, and their clinicopathological characteristics were compared by univariate analysis and multivariate logistic regression analysis.

Results: Univariate analysis showed that tumor size, pT stage, lympho-vascular invasion (LVI), estrogen (ER) status, hormone receptor (HR) status, and triple negative breast cancer (TNBC) were associated with SLN metastasis. However, pT stage, histological grade and TNBC were independent predictive factors for SLN involvement by multivariate logistic regression analysis.

Conclusions: Our study demonstrated that pT stage and histological grade provided positive, and TNBC provided negative prediction about SLN metastasis in early stage breast cancer patients with clinically negative axillary lymph nodes.

Keywords: Breast cancer; sentinel lymph node (SLN); clinicopathological characteristics; univariate and multivariate analysis

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Introduction

Breast cancer is now the most common cancer in Chinese women, and the leading cause of cancer death in women younger than 45 years (1,2). Axillary lymph node status is one of the most valuable predictors for the survival of breast cancer patients (3,4). Axillary lymph node dissection (ALND) has been accepted as the standard surgical treatment for breast cancer patients, and made great sense in assessment of lymph nodes status and regional tumor control (5). However, sentinel lymph node biopsy (SLNB), as a minimally invasive surgery, has become the alternative treatment of conventional ALND, especially for the patients with clinically negative axillary lymph nodes (6-8). Although SLNB has some advantages such as better cosmetic results, less limb complications and more rapid intraoperative diagnosis, it is also an invasive procedure with complications. Moreover, the reported incidence of

sentinel lymph node (SLN) metastasis varies from 22–40% (9-11), which means nearly 60–78% patients suffered from unnecessary invasive axilla surgery. It becomes important that whether we could make a predictive model to determine appropriate patients who might avoid SLNB and unnecessary surgery. Since the predictive factors affecting the SLN status have not been clarified yet, we performed this study to identify the clinicopathological predictors of SLN involvement.

Methods

Ethics statement

This study was approved by the Ethics Committee of the Peking Union Medical College Hospital, Chinese Academy of Medical Sciences.

Patients and clinicopathological characteristics

Our retrospective study analyzed consecutive patients who were diagnosed as early invasive breast cancer without clinically detected axillary lymph nodes and underwent breast surgery and SLNB in Department of Breast Surgery, Peking Union Medical College Hospital (PUMCH), between January 2014 and December 2016. In total, 324 patients were finally enrolled in this study. All patients' formalin-fixed paraffin-embedded (FFPE) pathological sections were reviewed to confirm the diagnosis, and the clinicopathological characteristics were collected thoroughly.

SLNB

SLNB was performed through both the methylene blue dye and the indocyanine green (ICG) (12,13) injection to the subareolar zone, minimal 10 minutes before the biopsy. Blued nodes were detected and excised with their lymphatic vessel, and double checked with fluorescence device. The SLN was diagnosed by the intraoperative frozen pathological section and was finally determined by the FFPE examination. ALND was the necessary procedure in case of detection of SLN metastasis.

Statistic analysis

As for detecting predictors of SLN metastasis, the quantitative variables were compared with *t*-test and the categorical variables were compared with chi-square tests or Fisher's exact test. Then multivariate logistic regression analysis was performed to test the independent predictors for all related clinicopathological characteristics from the univariate analysis (14,15). The significance threshold was set at $P<0.05$. Meanwhile, the odds ratio (OR) and 95% confidence intervals (CI) were also counted. SPSS software, version 20.0 (SPSS, Inc. Chicago, IL, USA) was used for all of the statistical analyses.

Results

Descriptive information of the study cohort

A total of 324 breast cancer patients underwent breast surgery and SLNB in our study. All patients were female, and all the clinicopathological characteristics were showed (*Table 1*). As for the SLNB, totally 1,334 SLNs were excised, with the average number 4.12±2.82. Sixty-six of 324 patients had positive SLN and received following ALND, which indicated our incidence of SLN metastasis was 20.4%. Of these 66 patients, 61 (92.4%) had macro-metastasis, 3 (4.6%) had micro-metastasis and 2 (3.0%) had isolated tumor cell (ITC).

Univariate analysis between clinicopathological characteristics and SLN status

According to the univariate analysis, our study found that tumor size, pT stage, lympho-vascular invasion (LVI), estrogen receptor (ER) status, hormone receptor (HR) status, and triple negative breast cancer (TNBC) were associated with SLN metastasis. Compared to patients with negative SLN, patients with positive SLN had bigger tumor size (2.017±1.236 *vs.* 1.646±1.114, P=0.019), higher pT stage (P=0.027), more LVI (7.6% *vs.* 2.3%, P=0.036), more ER positive cancer (90.9% *vs.* 77.1%, P=0.041), more HR positive cancer (92.4% *vs.* 79.0%, P=0.040), and less TNBC (3.0% *vs.* 13.2%, P=0.019) (*Table 2*).

Multivariate logistic regression analysis for the predictors of SLN metastasis

All the related clinicopathological characteristics from the univariate analysis ($P<0.20$), including tumor size, pT stage, histological grade, LVI, ER status, progesterone receptor (PR) status, HR status, immunophenotype and TNBC status, were calculated in the multivariate logistic regression analysis by forward stepwise method. Finally, histological

Table 1 The clinicopathological characteristics of early breast cancer patients

Characteristics	Numbers (n)	Percentage (%)
Age at diagnosis (years)		
<50	232	71.6
≥50	92	28.4
Laterality		
Left	155	47.8
Right	157	48.5
Bilateral	12	3.7
Surgery		
BCS	210	64.8
Mastectomy	114	35.2
pT		
T1a	31	9.6
T1b	59	18.2
T1c	159	49.1
T2	70	21.6
T3	5	1.5
Histological type		
Invasive	303	93.5
Invasive + carcinoma *in situ*	21	6.5
Histological grade		
Low grade	46	14.2
Medium grade	175	54.1
High grade	75	23.1
Unknown	28	8.6
LVI		
No	313	96.6
Yes	11	3.4
ER		
Negative	62	19.1
Positive	259	80.0
Unknown	3	0.9
PR		
Negative	73	22.5
Positive	248	76.6
Unknown	3	0.9
Hormone receptor		
Negative	56	17.3
Positive	265	81.8
Unknown	3	0.9
Her2 status		
Negative	254	78.4
Positive	54	16.7
Unknown	16	4.9
Ki67		
<14%	99	30.6
≥14%	222	68.5
Unknown	3	0.9
Immunophenotype		
Luminal A	74	22.8
Luminal B	181	55.9
Her2	21	6.5
TNBC	36	11.1
Unknown	12	3.7

BCS, breast conserving surgery; Her2, human epidermal growth factor receptor-2; LVI, lympho-vascular invasion; ER, estrogen receptor; PR, progesterone receptor; TNBC, triple negative breast cancer.

grade, pT stage and TNBC status were the independent predictive factors (*Table 3*).

Discussion

Since SLNB could appropriately assess axillary lymph node status, it has been demonstrated as the technical standard surgical procedure instead of ALND for the breast cancer patients with clinically negative axilla (6,7,16). Even though SLNB has fewer postoperative morbidity than that of ALND, it is reported that SLNB accounted for about 7–15% incidence of upper limb lymphedema, or 8–16% incidence of sensory loss or pain (17-19). Moreover, preoperative prediction of SLN status with various clinicopathological characteristics might avoid

Table 2 Univariate analysis between clinicopathological characteristics and SLN status

Characteristics	No. (%) of patients		P value
	SLN negative	SLN positive	
Total: 324	258	66	
Age (years)			
Mean ± SD	49.15±9.66	48.83±11.26	0.820
Age at diagnosis			0.489
<50	187 (72.5)	45 (68.2)	
≥50	71 (27.5)	21 (31.8)	
Laterality			0.382
Left	128 (49.6)	27 (40.9)	
Right	120 (46.5)	37 (56.1)	
Bilateral	10 (3.9)	2 (3.0)	
Surgery			0.275
BCS	171 (66.3)	39 (59.1)	
Mastectomy	87 (33.7)	27 (40.9)	
Tumor size			*0.019*
Mean ± SD	1.646±1.114	2.017±1.236	
pT			*0.027*
T1a	28 (10.9)	3 (4.5)	
T1b	52 (20.1)	7 (10.6)	
T1c	121 (46.9)	38 (57.7)	
T2	55 (21.3)	15 (22.7)	
T3	2 (0.8)	3 (4.5)	
Number of total SLN			
Mean ± SD	4.20±2.909	3.79±2.446	0.289
Histological type			0.474
Invasive	240 (93.0)	63 (95.5)	
Invasive + carcinoma *in situ*	18 (7.0)	3 (4.5)	
Histological grade			0.165
Low grade	42 (16.3)	4 (6.1)	
Medium grade	138 (53.5)	37 (56.1)	
High grade	56 (21.7)	19 (28.8)	
Unknown	22 (8.5)	6 (9.0)	
LVI			*0.036*
No	252 (97.7)	61 (92.4)	
Yes	6 (2.3)	5 (7.6)	

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	No. (%) of patients		P value
	SLN negative	SLN positive	
ER			*0.041*
Negative	56 (21.7)	6 (9.1)	
Positive	199 (77.1)	60 (90.9)	
Unknown	3 (1.2)	0 (0.0)	
PR			0.172
Negative	63 (24.4)	10 (15.2)	
Positive	192 (74.4)	56 (84.8)	
Unknown	3 (1.2)	0 (0.0)	
HR			*0.040*
Negative	51 (19.8)	5 (7.6)	
Positive	204 (79.0)	61 (92.4)	
Unknown	3 (1.2)	0 (0.0)	
Her2 status			0.849
Negative	202 (78.2)	52 (78.7)	
Positive	44 (17.1)	10 (15.2)	
Unknown	12 (4.7)	4 (6.1)	
Ki67			0.625
<14%	80 (31.0)	19 (28.8)	
≥14%	175 (67.8)	47 (71.2)	
Unknown	3 (1.2)	0 (0.0)	
Immunophenotype			0.119
Luminal A	60 (23.3)	14 (21.2)	
Luminal B	137 (53.1)	44 (66.8)	
Her2	18 (7.0)	3 (4.5)	
TNBC	34 (13.2)	2 (3.0)	
Unknown	9 (3.5)	3 (4.5)	
TNBC			*0.019*
TNBC	34 (13.2)	2 (3.0)	
Non TNBC	224 (86.8)	64 (97.0)	

P values in italic form indicate statistical significance. SLN, sentinel lymph node; HR, hormone receptor.

Table 3 Multivariate logistic regression analysis for the predictors of SLN metastasis

Predictors	OR	95% CI	P value
Histological grade	1.415	1.004–1.996	*0.048*
pT stage	2.169	1.065–4.417	*0.033*
TNBC	0.506	0.307–0.835	*0.008*

P values in italic form indicate statistical significance. OR, odds ratio; CI, confidence intervals.

the unnecessary SLNB in selected patients, which could consequently save more medical resources.

In our study, we used dual tracer method with methylene blue dye and ICG, and identified the average of 4.12 SLNs per participants, which demonstrated that SLNB with blue dye and fluorescence is a reliable and effective surgical technique. What's more, the detection rate of positive SLN was 20.4% in the present study, which was lower than that in previous ones (9-11). This discordance may be a result of more pT1 stage patients, which comprised 76.9% in our study and higher than about 50–60% in other studies.

Therefore, it brings the tumor size to us as the first and most common predictor for SLN metastasis. Previous literatures that the possibility of SLN or/and axillary lymph node involvement increased with the accretion of tumor (20-22). In the present study, we figured out the same opinion, which is that pT stage is the independent predictive factor of SLN metastasis in patients with early breast cancer (adjusted OR =2.169, 95% CI, 1.065–4.417, P=0.033), according to both univariate and multivariate analyses.

Secondly, in previous studies, histological grade was shown an important predictor, which was even more valuable than tumor size (23-25). Similarly, we found that histological grade had no significant difference between these two groups by univariate analysis (P=0.165), but it was demonstrated as the predictive factors of SLN positivity by multivariate analysis (adjusted OR =1.415, 95% CI, 1.004–1.996, P=0.048).

In addition, the role of TNBC that played in the SLN metastasis has been controversial. As we all know, TNBC compromised about 10–20% of all breast cancers, and exhibited more aggressive clinical behavior, higher metastatic potential and poorer prognosis when compared to other immunophenotype (26-28). However, the final result in our study figured out that TNBC was a negative predictor of SLN involvement, with adjusted OR as 0.506 (95% CI, 0.307–0.835, P=0.008). This conclusion was supported by many scholars who have identified that TNBC were associated with low incidence of axillary lymph node metastasis, and suggested that the poor biological features of TNBC might be not associated with lymphatic spread (29-31).

Besides these three predictive clinicopathological characteristics, young age at diagnosis, the presence of LVI, high Ki67 values, overexpression of Her-2 and other factors had been selected as the predictor affecting SLN metastasis in early breast cancer patients (32-37).

Our study had several limitations. Firstly, this was a retrospective study with relatively small sample size in single institution. We should recruit more participants for a new randomized, double-blind, multicenter clinical trial to verify the truth in the near future. Secondly, not all the detailed clinicopathological characteristics were collected through the patients' medical record which was due to the limitation of data storage system. More details should be reviewed if possible. Last but not least, although exact pathological evaluation of all tumor and SLN FFPE specimens was reviewed by experienced breast pathologists, there were still some time or technical limitations in detection of more biomarkers for all pathological sections, such as EGFR, CK 5/6 or androgen receptors, etc. If we could get more about these details, it maybe provides us more interesting and useful information.

Conclusions

In conclusion, our study demonstrated that pT stage and histological grade provided positive, and TNBC provided negative prediction about SLN metastasis in early stage breast cancer patients with clinically negative axillary lymph nodes. In spite of the limitations, the results are useful in clinical practice. We should run more clinical trials to optimize the precise predictive factors or models, in order that more patients could not suffer from ALND, or even SLNB in the future.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.10.20). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics

Committee of the Peking Union Medical College Hospital, Chinese Academy of Medical Sciences. Since this is a retrospective study without any intervention or treatment to patients, the Ethics Committee Board just approved it without giving an ID. Informed consent was waived.

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