False-negative Frozen Section of Sentinel Lymph Node Biopsy in a Chinese Population with Breast Cancer

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Abstract. *Aim: This study aimed to investigate the accuracy of frozen section (FS) in diagnosis of sentinel lymph node metastasis and to analyze the predictive factors for false-negativity. Patients and Methods: Patients with breast cancer and clinically negative axillary were recruited for sentinel lymph node biopsy (SLNB). All nodes were examined by intraoperative FS and underwent further paraffin sectioning. Results: A total of 1,272 patients underwent SLNB over an 8-year period, and 53 patients had false-negative FS. Univariate and multivariate analysis revealed that younger age, stellate mammographic pattern, and ER-positive status were statistically different when compared to the 53 members of the cohort who were truly negative on SLNB (control group). Eight patients were lost to clinical follow-up; the recurrence-free survival rate of the remaining 49 patients with false-negative SLNB did not differ from that of the 49-patient cohort (control group) (p=0.072), while these patients did experience poorer overall survival (p=0.035). Conclusion: Younger age, stellate mammographic pattern and ER-positive status were independent predictors for false-negative FS on biopsy.*

Sentinel lymph node biopsy (SLNB) is a reliable method for evaluating the lymph node status of the axillary, making standard axillary lymph node dissection (ALND) unnecessary. SLNB reduces morbidity from unnecessary ALND in patients who are axillary node-negative (1). Although the need for ALND for all cases of SLN metastases is being challenged, current guidelines still advocate it. Hence a rapid and accurate intraoperative analysis of SLNs is vital in order to reduce the need for reoperations in patients with SLN-positive breast cancer.

Among the various methods of intraoperative SLN assessment described, frozen section (FS) is the most commonly used. Current practice for intraoperative analysis of SLNB samples varied in a pan-European survey of 240 Units, 69.7% used FS, 11.7% using FS and imprint cytology (IC), and 11% used IC alone (2). According to a 2011 review, FS sensitivity ranges from 57 to 74% and specificity from 99 to 100% (3). The main objective of the current study was to determine the accuracy of intraoperative FS in diagnosis of SLN metastasis by examining the sensitivity, specificity and false-negative rate, and then analyzing the influential factors and prognosis.

Patients and Methods

Patient history. The study protocol was approved by the Hospital Human Ethical Committee (201509). Informed consent had been obtained from all patients before surgery. A retrospective review was performed of 1,272 patients who successfully underwent SLN biopsy at our Institute from January 2006 to October 2014. All patients had histopathological diagnosis of breast cancer and clinically negative axillary. Patients who received neoadjuvant chemotherapy were excluded. A total of 53 randomly selected patients through isometric sampling from known SLN-negative cases were set as the control group. The mammographic appearance of the invasive tumours in the current study was classified as stellate mammographic pattern and malignant calcification (4). The medical records of the patients were retrieved from our registry and their clinicopathological characteristics, treatment and prognosis were analysed.

Sentinel lymph node biopsy. SLN mapping was performed by using lymphoscintigraphy with methylene blue dye. On the day of operation, technetium 99 sulfur colloid (Beijing Shihong Pharmaceutical Development Center, Beijing, China) was injected intradermally above the tumour, peritumourally, in the areola of the breast or at the surgical site of previous biopsy. Scans of the

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Key Words: Breast neoplasms, sentinel lymph node biopsy, frozen section, false-negative reaction, predictive value of tests.

involved breast and axillary were acquired 2 h after tracer injection. Methylene blue dye (Jumpcan, Taixing, China) was injected 15 min before surgery. During surgery, the SLN was localized by using a Neo2000 gamma probe (Neoprobe Corporation, Dublin, Ohio USA). The SLN was defined as a blue lymph node or a lymph node with an *ex vivo* radioactive count≥10% of the *ex vivo* radioactive count of the hottest lymph node. In addition, any clinically suspicious, palpable lymph nodes were also removed.

Pathological examinations. All SLNs were subjected to standard FS evaluation with haematoxylin and eosin (H&E)-stained section. The first SLN defined as the bluest or the hottest lymph node was bisected longitudinally and frozen separately; other SLNs were frozen intact. FS were taken with a microtome setting of 4 μm. The remaining nodal tissue was fixed in 10% formalin and embedded in paraffin. After this fixation, serial sections were made of the SLN for definitive analysis. Macrometastases were defined as those having a diameter greater than 2 mm, micrometastases as those having a diameter between 0.2 and 2 mm, and isolated tumor cells (ITCs) as single tumor cells or small clusters of cells (diameter <0.2 mm). Specimens were considered to be human epidermal growth receptor 2 (HER2)-positive when they scored +3 by immunohistochemistry or were positive by fluorescent *in situ* hybridization. According to different combinations of estrogen receptor (ER), progesterone receptor (PR), HER2 status and Ki67, patients were categorized into four subgroups as follows: luminal A, luminal B, HER2-overexpressing, and triple-negative (5).

Statistical analyses. Statistical analyses were performed by using SPSS 19.0 (IBM Corporation, Armonk, NY, USA). Chi-square test, Fisher's exact test and analysis of variance were used to compare patient and tumor characteristics. Multivariate analyses were performed on variables with $p<0.05$ from the univariate analyses by logistic regression. Survival rates were calculated by the Kaplan–Meier method, and statistical significance was determined by log-rank test. A *p*-value of 0.05 or smaller was considered statistically significant.

Results

The accuracy of intraoperative FS. Of these 1,272 patients, FS of the SLNs were positive in 294 cases and negative in 978 cases. Of these 978 patients with an intraoperative-negative SLNB, 53 patients were postoperatively diagnosed as having a metastatic tumour in the SLN and the remaining 925 patients were negative by H&E-stained sections. The false-negative rate was 15.3%, giving FS a sensitivity of 84.7%, with specificity of 100.0% and accuracy of 95.8% (Table I). A total of 294 patients intraoperatively diagnosed as having positive SLNs underwent an immediate ALND. Of the 53 patients with false-negative FS, nine (17.0%) patients had macrometastases, 33 (62.3%) patients had micrometastases and 11 (20.8%) patients had ITCs.

Factors predictive of false-negative FS. Univariate analysis revealed that younger age, stellate mammographic pattern, ER positive and PR positive status were significantly associated with false-negative diagnosis when compared to the control group) which was negative for SLNB ($p<0.034$) (Table II). The percentage of HER2-positive patients in the false-negative group was significantly lower than that of the control group but the difference was not statistically significant ($p=0.070$).

Table I. *Results of frozen sections of sentinel lymph node.*

		Paraffin section, n		
		Positive	Negative	Total
Frozen section, n	Positive	294	0	294
	Negative	53	925	978
	Total	347	925	1272
Sensitivity,		294/347=84.7%		
Specificity		925/925=100.0%		
False-negative rate		53/347=15.3%		
Negative predictive value		925/978=94.6%		
Accuracy		(294 +925)/1272=95.8%		

Multivariable logistic regression analysis using backward stepwise method identified younger age, stellate mammographic pattern and ER-positive status as independent predictors for false-negative diagnosis ($p<0.046$). Of these variables, stellate mammographic pattern was the strongest predictor (odds ratio=3.9, 95% confidence interval=1.1-13.9, $p=0.021$; Table III).

Non-SLN status in patients with false-negative result. Of these 53 patients with false-negative results, 32 were treated with modified radical mastectomy and 21 with breast-conserving surgery. A total of 45 patients with false-negative results subsequently underwent different levels of ALND. Only four (8.9%) patients who had macrometastases in SLNs had non-SLN metastases in their ALND specimens, while the remaining 41 (91.1%) patients had only SLN metastases (Table IV). The other eight patients did not undergo ALND despite having false-negative FS. They opted for no further surgery after being counselled about the risks and benefits of ALND.

Other treatment and follow-up. Post operation, chemotherapy, radiotherapy and endocrine therapy were more frequently performed for the 53 patients with false-negative results than for those of the control group. These differences were statistically significant (Table II).

Follow-up was undertaken in 49 patients with false-negative SLNBs and 49 with negative SLNBs (control group), and eight patients were lost to follow-up. With a median follow-up of 39 months (range=13-93 months), only one patient in the false-negative SLNB group exhibited recurrence in the axillary nodes. The tumour in this patient was triple-negative and the patient did not receive radiotherapy. The recurrence-free survival rate (including no

Table II. *Clinical and pathological features of patients with breast cancer with intraoperative false-negative sentinel lymph node biopsy (SLNB) and those with true-negative SLNB.*

Characteristic	False-negative		True-negative		*p*-Value
	Number	%	Number	%	
Total	53		53		
Age, years					
≤35	8	15.09	2	3.77	0.011
>35-<65	42	79.25	39	73.58	
≥65	3	5.66	12	22.64	
Tumor location					
Upper outer quadrant	22	41.51	25	47.17	0.627
Upper inner quadrant	19	35.85	18	33.96	
Lower inner quadrant	0	0.00	2	3.77	
Lower outer quadrant	8	15.09	6	11.32	
Central area	4	7.55	2	3.77	
Tumor size					
T1	35	66.04	40	75.47	0.286
T2	18	33.96	13	24.53	
Malignant calcification					
Negative	33	64.71	36	69.23	0.625
Positive	18	35.29	16	30.77	
NA	2		1		
Stellate mammographic pattern					
Negative	38	74.51	47	90.38	0.034
Positive	13	25.49	5	9.62	
NA	2		0		
Histological type					
Infiltrating ductal carcinoma	49	92.45	46	86.79	0.339
Other type	4	7.55	7	13.21	
Nuclear grade					
Grade 1	12	26.67	13	28.26	0.986
Grade 2	23	51.11	23	50.00	
Grade 3	10	22.22	10	21.74	
NA	8		7		
Estrogen receptor					
Negative	8	15.09	21	39.62	0.005
Positive	45	84.91	32	60.38	
Progesterone receptor					
Negative	11	20.75	24	45.28	0.007
Positive	42	79.25	29	54.72	
HER2					
Negative	46	90.20	40	76.92	0.070
Positive	5	9.80	12	23.08	
NA	2		1		
Ki67%					
<14%	20	45.45	25	49.02	0.729
≥14%	24	54.55	26	50.98	
NA	9		2		
Molecular subtype					
Luminal A	24	47.06	18	34.62	0.127
Luminal B	19	37.25	16	30.77	
Triple-negative	6	11.76	10	19.23	
HER2+	2	3.92	8	15.38	
NA	2		1		
P53					
Negative	16	40.00	28	56.00	0.131
Positive	24	60.00	22	44.00	
NA	13		3		
Surgery					
Breast-conserving	21	39.62	18	33.96	0.546
Total mastectomy	32	60.38	35	66.04	
Chemotherapy					
Yes	39	78.00	27	55.10	0.016
No	11	22.00	22	44.90	
NA	3		4		
Radiotherapy					
Yes	23	46.94	14	28.00	0.027
No	26	53.06	36	72.00	
NA	4		3		
Endocrine therapy					
Yes	41	85.42	29	59.18	0.004
No	7	14.58	20	40.82	
NA	5		4		

NA: Not available; HER2: human epidermal growth factor receptor 2.

local recurrence or distant metastasis) for the 49 patients with false-negative SLNB did not differ from that of the 49-patient control group (p=0.072, Figure 1), while the patients with false-negative SLNB did have a poorer prognosis. The overall survival was statistically different between these two groups (p=0.035, Figure 2).

Discussion

SLNB is a minimally invasive procedure to determine the presence of ALN metastases in patients with clinically negative nodes. Although patients undergoing ALND have higher morbidity than that associated with SLNB, current guidelines still advocate ALND if SLN metastases are found, except for patients that fit the American College of Surgeons Oncology Group Z0011 criteria (6). An accurate intraoperative diagnosis of SLN metastases is therefore very important in order to avoid reoperation for patients with positive SLNs and spare them additional costs.

Among the various methods of intraoperative SLN assessment, FS is the most commonly used. Many studies have evaluated the sensitivity and accuracy of intraoperative FS. A meta-analysis reported sensitivity of intraoperative FS, ranging from 57-74% (3). According to another meta-analysis (7), the mean sensitivity was 73%, mean specificity 100%, and intraoperative FS was more reliable for detecting

Table III. *Multivariate analysis of factors affecting false-negative results of sentinel lymph node biopsy.*

Variable	OR	95% CI	*p*-Value
Age			0.009
≥65	1	Reference	
>35-<65	6.0	1.4-25.9	0.016
≤35	43.2	3.3-558.4	0.004
Stellate mammographic pattern			
Negative	1	Reference	
Positive	3.9	1.1-13.9	0.034
ER			
Negative	1	Reference	0.046
Positive	2.7	1.0-7.2	
PR			
Negative	1	Reference	
Positive	1.3	0.4-4.8	0.688

OR: Odds ratio; CI: confidence interval.

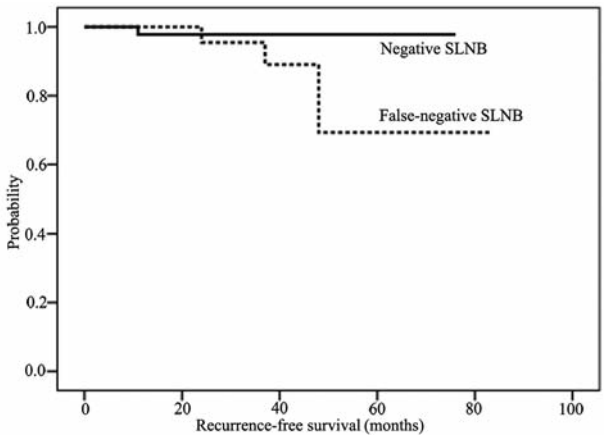

Figure 1. *The recurrence-free survival rate of the patients with false-negative sentinel lymph node biopsy did not differ from that of patients who had a truly negative SLNB (p=0.072).*

Table IV. *Non-sentinel lymph node (SLN) status in patients with false-negative SLN biopsy.*

Dissection	SLN metastasis (n)	Non-SLN metastasis (n)		
		Level I	Level II	Level III
SLN only	8	-	-	-
SLN+ level I	27	0	-	-
SLN+ level I & II	2	0	0	-
SLN+ level I, II & III	16	4	0	0

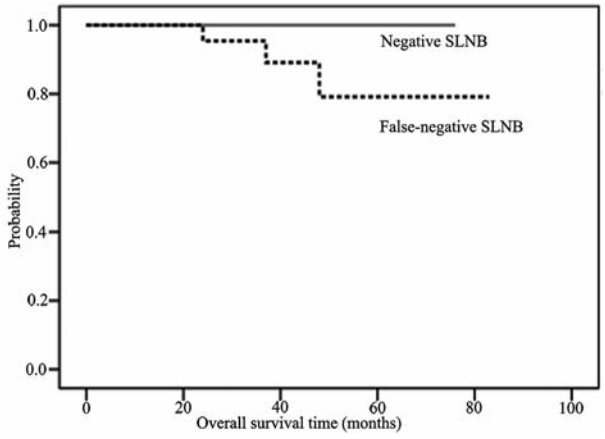

Figure 2. *The overall survival was statistically different between patients with false-negative sentinel lymph node biopsy (SLNB) and those with truly negative SLNB (p=0.035).*

macrometastases than for detecting micrometastasis/ITC deposits (7, 8). In addition, the touch IC method was also used widely. The greatest advantage of touch IC lies in its technical simplicity, low cost and total tissue preservation. But an accurate interpretation of the imprint is often limited by low cell yield and requires a pathologist experienced in cytological analysis. A meta-analysis that evaluated intraoperative IC for SLNs indicated that the pooled sensitivity was 63%, and its specificity was 99% (9). Hence FS evaluation is slightly superior to touch IC because it is more sensitive and less likely to produce an equivocal inconclusive result. Intraoperative FS may be the most desirable method for experienced teams of surgeons and pathologists (10). Molecular techniques such as ultrarapid immunohistochemistry using antibodies to cytokeratin, reverse transcription- polymerase chain reaction and one-step nucleic acid amplification analysis have also been used to facilitate detection of nodal metastasis especially for the detection of micrometastases (11, 12). However, the sensitivity of molecular techniques remains limited by the number of sections available/required for analysis, and a false-negative result is still possible because examination of every level of the entire SLN is infeasible. The possibility of contamination with RNA and the lack of morphological validation have raised questions about the clinical significance of a positive result. Multiple step-section FS analysis of SLNs is a relatively cost-effective alternative to molecular technologies and more accurate than standard FS or touch-prep cytology. But its disadvantage lies in the fact that a large number of scientists and consultants may be required in order to process multiple lymph nodes within a reasonable time (13). For these reasons, neither IC,

molecular techniques nor multiple step-section FS was routinely used in our Institute.

As outlined above, FS is now the preferred method for the detection of nodal metastases. However, the greatest drawback is the frequency of false-negative results because of which these patients are still subject to recall for ALND. Some reports revealed false-negative rates of FS ranging from 13% to 43% (14, 15) and false-negative results occurred more frequently in cases with micrometastases (15-18). In our study, FS had a false-negative rate of 15.3%, and 83.0% of metastasis were less than 2 mm in size. Although this was lower than most studies, we believe that if all SLNs were bisected longitudinally for diagnosis separately it might be more effective in reducing the false-negative rate.

Which factors can predict SLN metastasis and false-negative FS? Univariate and multivariate analyses showed that tumour size, location, type and lymphovascular invasion (LVI) were independent predictors of SLN metastasis (19). Another study revealed that LN-positive tumours were most frequent in the younger age group (<50 years). Among the immunohistochemistry-based individual biomarkers (ER, PR, Ki-67, HER2), only HER2 status was significantly predictive of lymph node status (20). Different breast cancer molecular subtypes have different biological features. Van Calster *et al*. showed that triple-positive tumors are most likely to be lymph node positive (21). Luminal A and triple-negative breast cancers are the least likely to present with positive lymph nodes. The imaging findings can also predict lymph node metastasis and prognosis. Among tumours smaller than 1 cm and measuring 1.0-1.4 cm, fewer cases of positive lymph nodes occurred in those with stellate lesions (22). But Tabar *et al*.'s study revealed that positive nodes were found in 12.23% (45/368) of lesions in the group of patients with stellate tumour without calcifications compared with 11.81% (30/254) of lesions in the group comprising the other patterns combined (4). They also found that casting-type calcifications were associated with a positive lymph node status, poorer histological grade and an increased risk of death. Moreover, after clinical follow-up, patients with stellate tumours had a better survival prognosis than those with tumours with other patterns (4, 22).

A few studies have tried to determine the predictors of false-negative FS. For these false-negative cases, an invasive lobular histology and LVI were found to be independent predictors on multivariate analysis (14). Another study also reported a higher false-negative FS rate for invasive lobular compared with invasive ductal carcinoma (23). But at least one study reported comparable results (24). The reason may be that invasive lobular tumor cells resemble benign lymphocytes and histiocytes and are more easily missed because of their bland cytological features and discohesive infiltrative pattern (23). In the study of Takei *et al*. patients with an intraoperative, false-negative SLNB had a combination of favourable and unfavourable prognostic factors compared to patients with negative SLNB. The favorable prognostic factors were positive PR and low nuclear grade, while an unfavourable prognostic factor was positive LVI (25). A recent study revealed that non-ductal histological subtype, absence of LVI and the size of SLN metastasis were independent factors associated with a higher false-negative rate compared with true-positive cases (26). As in our study, the favourable prognostic factors were positive ER and PR status and an unfavourable prognostic factor was a young age. We also found a new predictor: stellate mammographic pattern. Patients with stellate mammographic pattern were more likely to have false-negative FS result. Why these two groups exhibit such different characteristics remains unclear.

Another question is whether these false-negative cases need reoperation. One study showed that 94% (31 out of 33 specimens) of metastatic foci were found in the subcapsular sinus of the lymph node in false-negative cases (26), which implied that lymph node dissection may be safely avoided. Of our 45 patients who underwent a further different level ALND, additional non-SLN metastases were found in only four (8.9%) patients. That is to say that most patients (91.1%) were not required to undergo an additional operation. With a median follow-up of 29 months, only one patient exhibited recurrence in the axillary nodes. Takei *et al*. showed that none of their 132 patients with intraoperative, false-negative SLNBs experienced recurrence in the axillary or other regional nodes, with a median follow-up period of 58.1 months (25). Based on these data, we believe ALND can be avoided in most cases with intraoperative false-negative SLNB, which is agreement with Takei *et al*. (25). We also found the false-negative FS cases had poorer prognosis than patients with true-negative SLN after clinical follow-up.

Radiotherapy can effectively control local recurrence. A meta-analysis showed that axillary radiotherapy might be an alternative strategy to ALND (27). Non-randomized studies have also shown that axillary radiotherapy might be an effective and safe alternative to ALND for the treatment of the axillary (28). From this point of view, axillary radiotherapy might be an effective strategy substitute for ALND for some high-risk patients with false-negative FS of SLN.

The limitations of this study include a small sample size, its retrospective nature, and the short follow-up time. Future prospective studies with a large sample size are needed to validate our findings.

In conclusion, FS was useful for the detection of nodal metastases in SLNs. The main failure of FS was in detection of micrometastases and ITCs. Younger age, stellate mammographic pattern and positive ER status were independent predictors for false-negative FS. ALND can be avoided in most patients with intraoperative, false-negative SLNB.

Acknowledgements

The Authors thank all staff members of the Department of Pathology who were involved in diagnosing our patients.

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Received January 4, 2016
Revised February 17, 2016
Accepted February 18, 2016