

Original Article

Analysis of false negative rate in sentinel lymph node biopsy of breast cancer: a single centre retrospective study from China

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Abstract: Sentinel lymph node biopsy substituting axillary lymph node dissection has become a routine surgery in many countries but not in China because of the false negative rate. False negative (FN) of sentinel lymph node (SLN) can lead an incorrect assessment of pathological staging. In this study, we retrospectively analyzed the clinic pathological data of 645 breast cancer patients in Shandong Cancer Hospital and Institute from January 2012 to December 2015. True positive (TP), True negative (TN) and FN were identified in 383 patients (59.4%), 215 patients (33.3%) and 39 patients (9.2%), respectively. Among FN patients, about 92.3% of them were found that the positive lymph nodes were in Level I and/or Level II. Negative predictive value was 96.4% (215/223). Accuracy rate was 92.7% (494/598). FN rate was likely to occur in patients who were estrogen receptor (ER) negative, progesterone receptor (PR) negative, human epidermal growth factor 2 (HER2) positive and less than 3 positive axillary lymph nodes (all $P < 0.05$). Among these four molecular subtypes, HER2-enriched subtype is more likely to be FN ($P = 0.001$). A multivariate logistic regression model confirmed that ER status ($OR = 0.124$, $P < 0.05$), HER2 status ($OR = 3.703$, $P < 0.05$) and the numbers of positive lymph nodes ($OR = 0.009$, $P < 0.05$) were all independent factors predicting FN results. For those patients with high risk factors, such as ER negative, PR negative and HER2 positive, dissection of Level I and Level II lymph node may be a relatively safe measure, considering the limited medical conditions, such as unskilled surgeons and poor equipment conditions.

Keywords: Breast neoplasm, sentinel lymph node biopsy, false negative, axillary lymph node dissection

Introduction

Breast cancer is the most common malignant tumor and the leading cause of cancer death in female patients. Lymph node metastasis is one of the most important prognostic factors in breast cancer and lymph node status is a major determinant of treatment strategy for early breast cancer. Sentinel lymph node (SLN) is defined as the first chain node in the lymphatic vessel which receives primary lymphatic flow. If the SLN is negative, then other nodes are expected to be disease-free. In order to decrease morbidity associated with lymph node dissection, such as limb edema, numbness and activity limitation, the technology of sentinel lymph node biopsy (SLNB) was first reported in the 1990s [1, 2]. Many labeling methods, such as blue dyes and radiocolloid tracers

alone or in combination, were introduced to identify the SLN. SLNB was accepted as a standard for T_{1-2} breast cancer undergoing breast surgery without clinical palpable lymph nodes after large clinical trials indicated considerably clinical benefit in many countries [3-6].

Many researchers have conducted follow-up studies to identify the significance of false-negative (FN) results [7, 8]. It is known that identification of lymph node status plays a far-reaching implication on postoperative management and adjuvant therapy in breast cancer. The FN rate defines the frequency with which the sentinel lymph nodes are pathologically negative but in the presence of other positive axillary nodes. In most area of China, SLNB rather than axillary lymph node dissection (ALND) is not a routine operation. Incomprehension of the axillary

False negative in sentinel lymph node biopsy of breast cancer

Table 1. Analysis of clinical and pathological characteristics of breast cancer patients

| Clinicopathology | N (%) |
|----------------------------|------------|
| Age at diagnosis | |
| >49 years | 272 (42.2) |
| ≤49 years | 373 (57.8) |
| Menopause status | |
| Post menopausal | 241 (37.4) |
| Premenopausal | 404 (62.6) |
| ER status | |
| Positive | 397 (61.6) |
| Negative | 248 (38.4) |
| PR status | |
| Positive | 376 (58.3) |
| Negative | 269 (41.7) |
| HER2 status | |
| Positive | 152 (23.6) |
| Negative | 493 (76.4) |
| Ki-67 expression | |
| ≥20% | 233 (36.1) |
| <20% | 412 (63.9) |
| Histopathological type | |
| Invasive ductal carcinoma | 548 (85.0) |
| Invasive lobular carcinoma | 65 (10.0) |
| Mucoid carcinoma | 11 (1.7) |
| Other types [†] | 21 (3.3) |
| Molecular subtypes | |
| Luminal A | 245 (38.0) |
| Luminal B | 202 (31.3) |
| HER2-enriched | 78 (12.1) |
| TNBC | 120 (18.6) |
| Tumor size (T, cm) | |
| T≤2 | 345 (53.5) |
| 2<T≤5 | 291 (45.1) |
| T>5 | 9 (1.4) |
| Positive lymph node | |
| 0 | 377 (58.5) |
| 1~3 | 180 (27.9) |
| 4~9 | 69 (10.7) |
| ≥10 | 19 (2.9) |
| TNM classification | |
| I | 188 (29.1) |
| II | 350 (54.4) |
| III | 107 (16.5) |

[†]adenoid cystic carcinoma (1/21); micropapillary carcinoma (4/21); mixed carcinoma (8/21); neuroendocrine carcinoma (2/21); cribriform carcinoma (3/21); apocrine carcinoma (2/21); signet ring cell carcinoma (1/21).

lymph nodes' status but avoiding ALND might lead to breast cancer's under-treatment, since

the accuracy of the status is a very important factor in the implementation of systemic treatments. For those patients with FN SLN who avoiding ALND, loco-regional disease control may be discounted. Therefore, it is important to minimize the FN rate of SLN if the patients intent to avoid ALND. The present study reviewed the results of SLNB at Shandong Cancer Hospital and Institute in China from January 2012 to December 2015. All suitable patients underwent SLN biopsy, and then ALND was carried out. The SLN and non SLN simultaneous removals were designed to evaluate the accuracy in prediction of the state of the axillary. True positive (TP) is defined as sentinel lymph node and axillary lymph node are all positive. In this study, we compared the FN and TP in order to determine the patients who are incline to be FN and to gain a better benefit in the process of surgical treatment.

Methods

The clinical and pathological data of 645 breast cancer patients were collected in Shandong Cancer Hospital and Institute in China from January 2012 to December 2015 and retrospectively analyzed. Eligibility criteria were illustrated as follows: (1) all patients received the ALND followed by SLNB; (2) no patients received neoadjuvant therapy; (3) the axillary had no previous surgical operation or radiotherapy; (4) the immunohistochemical indicators included ER, PR, HER2 and Ki-67. Breast cancer was then classified based on the cancer staging of American Joint Committee on Cancer (AJCC, 7th edition, 2010). The study was approved by the Ethics Committee of Shandong Cancer Hospital and Institute.

In this study, the streptavidin-peroxidase immunohistochemical method was used to detect the expression of ER, PR, HER2 and Ki-67. Cancer cells with nuclei positively stained by ER, PR, and Ki-67 were considered to be positive, while HER2-positive was observed in the cellular membrane or cytoplasm. ER- or PR-positive were defined by at least 1% of nuclei positively stained [9], while 20% of nuclei positively stained by Ki-67 could be regarded as high expression [10]. According to the guideline from the American Society of Clinical Oncology and College of American Pathologists, HER2 expression can be classified as HER2-positive (score 3+), suspected HER2-positive (score 2+) or HER2-negative (score 0 or 1+). For

False negative in sentinel lymph node biopsy of breast cancer

Table 2. Comparison of clinicopathology between FN SLN and TP SLN

| Clinicopathology | FN | TP | X ² | P-value |
|--------------------------------|----|-----|----------------|---------|
| Age at diagnosis | | | | |
| >49 years | 18 | 222 | | |
| ≤49 years | 21 | 161 | 2.013 | 0.156 |
| Menopausal | | | | |
| Postmenopausal | 17 | 192 | | |
| Premenopausal | 22 | 191 | 0.606 | 0.436 |
| ER status | | | | |
| Positive | 23 | 306 | | |
| Negative | 16 | 77 | 9.017 | 0.003 |
| PR status | | | | |
| Positive | 24 | 299 | | |
| Negative | 15 | 84 | 5.386 | 0.020 |
| HER2 status | | | | |
| Positive | 11 | 38 | | |
| Negative | 28 | 345 | 11.529 | 0.001 |
| Ki-67 status | | | | |
| >20% | 17 | 115 | | |
| ≤20% | 22 | 268 | 3.029 | 0.082 |
| Molecular subtype | | | | |
| Luminal A | 11 | 169 | | |
| Luminal B | 14 | 176 | | |
| HER2-enriched | 6 | 8 | | |
| TNBC | 8 | 30 | 28.079 | 0.001 |
| SLN detection method | | | | |
| Methylene blue | 10 | 107 | | |
| 99mTc-sulfur colloid | 11 | 134 | | |
| Combination method | 18 | 142 | 1.310 | 0.519 |
| Tumor size (T, cm) | | | | |
| T≤2 | 15 | 161 | | |
| T>2 | 24 | 222 | 0.186 | 0.666 |
| Number of positive lymph nodes | | | | |
| ≤3 | 27 | 146 | | |
| 4~9 | 11 | 176 | | |
| ≥10 | 1 | 61 | 15.175 | 0.001 |

those with suspected HER2-positive tumors, fluorescence in situ hybridization should be used to confirm their expression. According to the Expert Consensus of the 2013 St Gallen International Breast Cancer Conference [10], breast cancer can be divided into four molecular subtypes on the basis of their molecular markers. The typing criteria was as follow: (1) luminal A: ER-positive, PR≥20% [11], HER2-negative and Ki-67≤20%; (2) Luminal B (HER2-negative): ER-positive, HER2-negative, PR≥20% [11] or Ki-67>20%; (3) Luminal B (HER2-

positive): ER-positive and HER2-positive; (4) HER2-enriched: ER-negative, PR-negative, HER2-positive; (5) TNBC: ER-negative, PR-negative, HER2-negative.

Methylene blue (Jiangsu Jichuan Pharmaceutical Co., Ltd., H32024827) or Carbon Nanoparticles Suspension Injection (Chongqing Lummy pharmaceutical Limited by Share Ltd, H20073246) combined with 99mTc-sulfur colloid were used to search for SLN. 99mTc-sulfur colloid (0.5-1.0 mCi/0.5-2.0 ml) was subdermally injected into the cutaneous projection of the breast tumor 3-20 h before operation. Methylene blue (2 ml) or carbon nanoparticles suspension (1 ml) was injected to breast areola 15-30 min before operation. We used gamma-detecting probe to detect the SLN, and recorded the radiation intensity intraoperatively. Each radioactive lymph node with a probe count >10% comparing with the hottest node was removed as the SLN.

Statistical analysis

Data was analyzed using SPSS 17.0 software (SPSS Inc., Chicago, Illinois, USA). According to the criteria of Louisville University of SLNB technology, false negative (FN) rate = FN/(FN+TP); negative predictive value = true negative/ALN-negative; accuracy rate = (TP+true negative)/ALN-positive; test was used to compare the difference between two groups. Multivariate analysis was performed by using Logistic regression model. All tests were considered to be statistically significant when the *p* value was <0.05.

Results

General results

Between January 2012 and December 2015, a total of 645 patients underwent SLNB followed by ALND were illustrated in **Table 1**. The median age of the patients was 49 (range 26-80) years. Among the 645 patients, the median number of SLN identified was 4 (range 1-12). A positive SLN result was found in 391 patients (60.6%), a positive SLN and with axillary node metastasis was identified in 383 patients (59.4%) and FN SLN was found in 39 patients

False negative in sentinel lymph node biopsy of breast cancer

Table 3. A multivariate logistic regression model to analysis of SLN

| Subject | OR | 95% CI | P-value |
|-------------------------------|-------|--------------|---------|
| Stage at diagnosis | 0.977 | 0.899~1.063 | 0.591 |
| Menopausal status | 0.985 | 0.950~1.020 | 0.395 |
| ER status | 0.124 | 0.026~0.580 | 0.008 |
| PR status | 1.052 | 0.235~4.711 | 0.948 |
| HER2 status | 3.703 | 0.788~17.399 | 0.009 |
| Ki-67 status | 1.009 | 0.975~1.043 | 0.623 |
| Molecular subtype | 2.000 | 0.477~8.387 | 0.343 |
| Tumor size | 1.561 | 0.928~2.626 | 0.093 |
| Number of positive lymph node | 0.009 | 0.100~0.718 | 0.009 |

ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; SLN: Sentinel lymph nodes.

Table 4. Axillary lymph node status in breast cancer patients with negative SLN

| SLN-negative | | | Case number (%) |
|--------------|----------|-----------|-----------------|
| Level I | Level II | Level III | |
| + | - | - | 22 (56.4%) |
| - | + | - | 5 (12.8%) |
| - | - | + | 2 (5.1%) |
| + | + | - | 9 (23.1%) |
| + | - | + | 0 |
| - | + | + | 1 (2.6%) |
| + | + | + | 0 |

(9.2%). The number of patients with SLN-positive and ALN-negative was 8 (1.2%). True negative SLN was found in 215 patients (33.3%). Negative predictive value was 96.4% (215/223). Accuracy rate was 92.7% (494/598).

Correlation of FN SLN and TP SLN regarding clinical pathological characteristics

A significant difference was observed in FN in **Table 2** for ER negative ($P=0.003$), PR negative ($P=0.02$), HER2 positive ($P=0.001$), HER2-enriched subtype ($P=0.004$), less than 3 positive lymph node ($P=0.002$). No significant difference was found between FN and TP regarding age at diagnosis, menopause status, Ki-67 status and tumor size (all $P>0.05$). A multivariate logistic regression model confirmed that ER status (OR=0.124, $P<0.05$), HER2 status (OR=3.703, $P<0.05$) and the numbers of positive lymph nodes (OR=0.009, $P<0.05$) were all independent factors predicting FN results (**Table 3**).

Comparison of axillary lymph node metastasis in different levels

In those FN SLN patients, there were 56.4% of positive lymph node were occurred in Level I, 12.8% in Level II and 5.1% in Level III. Positives lymph nodes occurred in Level I and Level II were in 23.1%. When SLN was negative, Level I and/or Level II harbored metastases in 92.3% patients (**Table 4**).

Discussion

Sentinel lymph node biopsy has become an acceptable way of lymph node status staging in axillary-node-negative patients. Because ALND is potentially associated with marked morbidity, limb edema, numbness, activity limitation and some other complications, some have questioned whether ALND suitable for all breast cancer patients. With the increasing use of SLNB, FN SLN is a thorny problem to be faced. In many areas of China, SLNB technology is not a widely accepted method for several reasons such as exiting FN, equipment condition backwardness. According to the breast cancer treatment consensus, for those patients with negative SLN, they may escape from radiotherapy. FN SLN could be the source of future recurrence. Previous studies have reported that the FN rate of SLN was 4%-29% [12-16]. In this study, FN rate was 9.2%, which approached the average level compared with the majority of the reports. The varied false negative rate of SLN may be depending upon the surgeons' proficiency and detection method. In our research, the accurate rate in determining axillary lymph node status was 92.7%, which is close to Pargaonkar *et al.* [17] reported.

In this study, comparing FN with TP, FN was associated with ER and PR negative breast cancer. Andersson *et al.* [18] also have reported a higher FN rate (28%) in hormone receptor-negative patients. While Zabagno *et al.* [19] have reported a lack of correlation between ER/PR and FN rate. The different results may be owing to the judgment standard of ER and PR or ethnic difference. In the present study, HER2-enriched is inclined to be FN. The reason may be related to the aggression of cancer. The cancer embolus blocked lymphatic that can

False negative in sentinel lymph node biopsy of breast cancer

mislead the tracer normal drainage. Another reason may be due to the inability of macrophage to uptake the tracer, preventing the tracer from entering into the lymphatic system.

In our study, the more positive axillary lymph nodes were detected, the less possibility for SLN appeared to be FN. This result was consistent with most of the previous research reports [18, 20-22]. When the number of SLNs were 1, 2, 3 and 4, FN SLN rates were 30.5%, 23.1%, 14.3% and 4.5%, respectively. With the increasing number of SLN, the FN rate decreased. Previous study reported that when the SLN was more than 4, the diagnostic accuracy is significantly improved [23]. Our study showed that when SLN was up to 5, there was no FN eventually. We found no relationship with injection method, whatever methylene blue, ^{99m}Tc -sulfur colloid or in combination and this is consistent with Martin's [22] report.

According to the American College of Surgeons Oncology Group (ACOSOG) Z0011 test [24], based on the T₁₋₂ stage breast cancer patients, there were no significant differences on five-year survival of those patients no more than 2 positive SLN with or without ALND. While these patients experienced breast conserving surgery and went through postoperative radiotherapy. Due to clinical benefit and feasibility, SLNB replacement of ALND was becoming more popular in clinic [25]. Absolutely, it is important that the FN rate should be reduced, especially for those who have no opportunity to get postoperative radiotherapy. For those patients with FN, we found that most of the positive node located in Level I and Level II, and it is necessary to take axillary lymph nodes dissection of Level I and Level II in order to reduce the cancer residual if the surgeon is unskilled or equipment condition is backward.

Reducing the FN rate is the backbone of SLNB as a substitute operation, so we could omit axillary lymph node dissection. To achieve this goal, we must assure to evaluate the SLN accurately. The present study suggested that FN SLN was significantly related to ER, PR and HER2 status, molecular subtypes. In spite of negative SLN, the exploration of Level I and Level II lymph node status may be a relatively safe measure for those high-risk patients, considering the limited medical conditions, such

as unskilled surgeons and poor equipment conditions.

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Disclosure of conflict of interest

None.

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False negative in sentinel lymph node biopsy of breast cancer

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False negative in sentinel lymph node biopsy of breast cancer

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