Preoperative Tumor Biopsy Results In More Detected Sentinel Node Than Intraoperative Biopsy In Breast Cancer Patients

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ABSTRACT

Background Sentinel lymph node biopsy (SLNB) acts as a vital role in the breast cancer surgery, and the identified number of sentinel nodes

determines its accuracy to represent the status of axillae. There remain two tumor biopsy modes in breast cancer, preoperative and intraoperative biopsy. We compared the effect of the two different biopsies on the result of SLNB.

Methods Patients with clinical stage T1-3, N0 tumor were enrolled in this study. 53% received preoperative tumor biopsy and 47% received intraoperative excisional biopsy. For search of the sentinel lymph node, patients received dual tracer injection. The number of SLNs detected and false negative rate were compared between groups.

Results 204 patients were enrolled, 108 received preoperative tumor biopsy and 96 received intraoperative excisional biopsy. Among all the patients, 160 received ALND following SLNB. Preoperative tumor biopsy detected more SLNs than intraoperative biopsy (mean rank 113.87 vs. 90.9, p= 0.004). False negative rate in preoperative and intraoperative tumor biopsy was 3% and 18%, respectively.

Conclusions Patients in preoperative tumor biopsy group could find more SLNs than intraoperative biopsy patients. False negative rate was also lower in preoperative biopsy group.

Keywords Breast cancer; sentinel lymph node biopsy; preoperative tumor biopsy; intraoperative tumor biopsy

Introduction

As shown in the reports of Global Cancer Statistics 2018[1], breast cancer remained the most commonly diagnosed cancer and the leading cause of cancer death among females. It was estimated that there were about 2.1 million newly diagnosed female breast cancer cases one year, accounting for almost one quarter cancer cases among women[1].In the past, axillary lymph node dissection (ALND) was well accepted as a standard procedure in breast cancer surgery. It was not only a vital treatment means but could provide useful axillary staging information[2]. On the other hand, it is necessary to emphasize that ALND often cause several complications, such as wound infection, numbness, reduced shoulder mobility and lymphoedema of the arms[3]. Sentinel lymph node biopsy (SLNB) has

been accepted as a minimally invasive alternative to ALND, compared with ALND it can also improve the post-operative life quality[4,5]. Definition of sentinel lymph node (SLN) is the first axillary lymph node affected by a tumor. In 1993, Krag and his colleagues reported SLN mapping in breast cancer patients for the first time[6]. Since then, several studies have demonstrated the accuracy of SLNB in assessing the histological status of the axilla[7].Based on the results of large clinical trials, SLNB has been considered as the gold standard for clinically node-negative breast cancer patients[8].As reported in a collective review and a meta analysis[9,10], the overall false negative rate in breast cancer for SLN biopsy is 4% to 5%. More importantly, the 10-year follow up results of ACOSOG Z0011 trial demonstrated that SLND alone did not result in inferior overall survival outcomes compared with ALND for patients with clinical T1 or T2 node-negative breast cancer and 1 or 2 positive sentinel nodes treated with breast conservation therapy and adjuvant systemic therapy[11]. Therefore, patients with 1 or 2 positive sentinel lymph nodes can be free from ALND.

The number of SLNs identified at breast cancer operation is variable. According to the study of McCarter[12] et al., the number of SLNs per patient ranged from 1 to 8 (or more). More importantly, they also demonstrated that patients with more SLNs removed were

more likely to find a positive lymph node than those with fewer removed (35% versus 28%, p=0.023), indicating that more SLNs removed will minimize false negative results and represent axillary status more accurately.

Tumor biopsy is commonly performed for the determination of the characterization of suspected lesions. Considered as convenient and highly sensitive, tumor biopsy facilitates pathologic diagnoses and guides treatment options. For breast cancer, there exist two tumor biopsy modes: preoperative core needle biopsy and intraoperative excisional biopsy. Literally, preoperative tumor biopsy is performed before surgery and perhaps cause less damage to the anatomic structure of lymphatic channels than intraoperative excisional biopsy. To determine whether the two biopsy patterns impose different impact on the outcomes of SLNB, we made a comparative analysis in this paper.

Patients and Methods

Between 2016 and 2018, a total of 204 female invasive breast cancer patients were retrospectively enrolled in this study. Patients with clinical stage T1-3, N0 tumor were eligible. We retrieved medical records to obtain clinicopathologic features and treatment information. All patients underwent dual-tracer SLNB and radical mastectomy/breast conservation. Besides, a level I/II axillary

lymphadenectomy was performed in 160 patients. Among the 204 participants, 108 underwent preoperative core needle biopsy, while the following 96 underwent intraoperative excisional biopsy.

Sentinel Lymph Node Detection Technique

To search the sentinel lymph node, all patients received dual tracer (radiolabeled colloid and blue dye) injection. In detail, sulfur colloid was labeled with ^{99m}Tc after filtering through a Millipore filter with a pore size of 220nm (Beijing Atomic Galactic Jinan Drug Center, Beijing, China), then 18-37 MBq of ^{99m}Tc -labeled sulfur colloid was injected into the mammary gland at 6 and 12 o'clock of the areola surrounding area 3–18 hours before surgery.[13] Preoperative SPECT/CT lymphoscintigraphy (Philips Electronic N.V, Beijing, China) was performed before surgery. Blue dye (methylene blue) (2–4 mL) was injected subcutaneously around the tumor 10 minutes before the initiation of tracing SLNs.

Statistical Analysis

All statistical data were analyzed with SPSS version 22.0 software (IBM Corp., Armonk, USA). In the process of statistical analysis, we defined the number of identified SLNs into 3 ranks: 1-2, 3-4 and more than 5. Mann-Whitney U test was used for ranked data. Fisher's exact test was applied for comparison of false-negative rate between the two groups. Significance was determined at $p < 0.05$.

Results

Patient characteristics

In all, 204 consecutive patients were enrolled in this study, 108 patients (53%) received preoperative tumor biopsy and 96 (47%) received intraoperative excisional biopsy. Among all the patients, 160 received ALND following SLNB. The median age of patients was 51 years (range 27-79 years), the median number of SLN was 2 (range 1-10). A summary of the patient and tumor characteristics for all patients is included in Table 1. As shown in the table, most of the tumor (96%) was invasive ductal carcinoma, 4% was invasive lobular carcinoma. For tumor category, 107 patients were pT1, 86 were pT2, 11 were pT3.

Detected SLN number and false negative rate

Since the data of identified SLN numbers does not comply to normal distribution, ranked sum test was applied for the statistic analysis （Figure1） .The median number of identified SLN in preoperative biopsy patients and intraoperative patients was 3 and 2, respectively. Preoperative tumor biopsy detected more SLNs than intraoperative biopsy (mean rank 113.87 vs. 90.9, p= 0.004). Among the 160 patients underwent ALND, false-negative result was found in 9 patients, which indicated sentinel node was pathologically negative when other axillary nodes showed metastases. Thus, the SLNB of

these 9 patients failed to correctly predict the status of axillae. One of the 9 patients received preoperative biopsy and the remaining 8 patients belonged to intraoperative group. As shown in Table 2, in preoperative biopsy group, 35 out of the 75 patients (46%) who underwent axillary dissection had lymph node metastases. In these patients, SLNB correctly predicted the positive nodal status of the axilla in 34 patients (34/35, 97%). So, in this group the overall sensitivity was 97% (34/35) and the false-negative rate was 3% (1/35). As for intraoperative biopsy patients, among 85 patients underwent ALND, 44 patients (52%) showed axillary metastases. Out of the 44 patients, SLN metastasis was observed in 36 patients (82%) were, while the other 8 patients showed no tumor infiltrate in SLNs. In this group, sensitivity of SLN to identify metastases was 82% (36/44) and the false-negative rate was 18% (8/44). The difference in false-negative rate was significant between two groups (3% vs. 18%, p=0.039).

Subgroup analysis to find factors influencing the number of identified SLNs

Based on tumor location, patients were classified into 3 groups: tumor located in outer quadrant, inner quadrant and subareolar area. Then comparison was made in different subgroups. As shown in Table 3, in patients with tumor located in outer quadrant, preoperative

biopsy detected more SLNs than intraoperative biopsy (p=0.026). However, when tumor was located in inner quadrant or subareolar area the difference was not observed (p=0.101; p=0.166). When stratified by primary tumor category, we observed that in patients with T2 or T3 tumor, preoperative biopsy was associated with more identified SLNs (Table 4, p=0.002). Next, in respect to patient age, we found in patients older than 50 years, more SLNs could be detected in preoperative biopsy group as compared with intraoperative biopsy group(p=0.003). In patients younger than 50 years, no significant difference could be seen (p=0.342). Last, we aimed to find out whether time interval between preoperative biopsy and breast surgery had effect on the number of SLNs detected in SLNB.As shown in Table 6, when the duration was shorter than 7 days, preoperative biopsy group had more detected SLNs than intraoperative biopsy group. When the duration was longer than 7 days, preoperative and intraoperative biopsy imposed similar influence on identifying SLNs.

Discussion

Axillary lymph node dissection had been used in women with axillary nodal metastases for a long history. It was effective in maintaining regional control but also associated with significant risk of several complications such as lymphedema, numbness et al.[14]**.** As a less invasive alternative, SLNB has been gradually performed in

more breast cancer patients. Its efficacy has been verified in several large clinical trials. The ACOSOG Z0011 trial enrolled eligible patients with clinical T1 or T2 invasive breast cancer, no palpable axillary adenopathy, and 1 or 2 sentinel lymph nodes containing metastases[11].With a median follow up of 9.3 years, SLND alone was not inferior to ALND for both overall survival and disease-free survival. The NSABP B-32 trial also confirmed that regional control, overall survival and disease-free survival were equivalent between SLNB alone group and SLNB with axillary dissection group. Therefore, if applied properly, SLNB could benefit patients as ALND while induce less morbidity[15].

Meanwhile, we must emphasize the premise to choose SLNB rather than ALND is its accuracy in representing the status of the axilla. Only when the precision is guaranteed can SLNB be used to direct doctors to stage the axilla and design according treatment plan. We wondered whether intraoperative tumor biopsy would impose effect on the anatomy of lymphatic channels and lead to the SLN detection less reliable. In this regard, we studied the number of SLNs found during surgery and the false negative rates in preoperative and intraoperative tumor biopsy groups. All the enrolled patients underwent SLN biopsy using combined tracer of blue dye and radioisotope. Based on our results, preoperative tumor biopsy could

detect more SLNs than intraoperative biopsy. We attributed this disparity to the anatomy alteration of lymphatic channels caused by intraoperative excisional tumor biopsy. Since tumor excision during the surgery is more invasive than preoperative core needle biopsy, it may destroy the lymphatic channels seriously and result in less SLNs identified. The number of SLNs sent for histology test plays a significant role in evaluating the axillary status. One critical reason is the sentinel node number potentially associates with the risk of being unable to recognize a positive SLN. The study of Robbins[16] corroborated this theory, he demonstrated that the SLN positivity was in a significantly greater frequency when two or more SLNs were found as compared to when only a single SLN was found (34% versus 18%, P=0.003). Although several previous researches supported the significance of detecting all radioisotope or blue dye-containing lymph nodes and emphasized this concept from the "more is better" viewpoint, there was no consensus on how many SLNs must be removed to accurately predict lymph node status[16-18].One paper showed that removing up to 5 SLNs was adequate to find metastatic carcinoma in more than 99% of patients, indicating that the surgeon can stop the dissection after removing 5 SLNs[19]. However, the data of another paper found although 98% of positive SLNs were identified within the first three SLN sites, the rest patients had their

first positive SLN at sites 4 to 8. So that authors suggested there was no absolute upper threshold for the number of SLNs that should be removed and SLN biopsy should be performed until all hot nodes detected and removed. Robbins also favored the attempts to identify all potential SLNs to avoid failure in recognizing a positive SLN[16]. In our study, since a part of the recruited patients underwent axillary lymph node dissection, we could verify the accuracy of SLNB. We observed in preoperative and intraoperative biopsy group, the false negative rate of was 3% and 18% (p=0.039), respectively. So that our results were in accordance with other researches, which favored that the false negative rate decreased as the number of removed SLNs increased. For instance, one study[21] showed that the false negative rate was 26.6% for a single SLN, while it decreased to 0% when 4 or more SLNs were removed.

As shown above, with regard to identified SLN number, patients could benefit more from preoperative tumor biopsy. Furthermore, we made subgroup analysis when taking several clinical parameters into consideration. Tumor position, T stage, patient age, duration between tumor biopsy and breast surgery were included in subgroup analysis. We found when tumor located in outer quadrant, T2 or T3, patient older than 50 years, difference in identified SLNs numbers between preoperative biopsy group and intraoperative group was

significant. Therefore, we suggest under the above conditions, preoperative tumor biopsy is superior than intraoperative biopsy. Besides, we emphasize the necessity to make preoperative tumor biopsy as the first choice when there were less than 7 days between biopsy and breast surgery.

Since when the interval was longer than 7 days, no significant difference in the number of SLN could be seen.

In conclusion, we observed that preoperative tumor biopsy could detect more SLNs than intraoperative tumor biopsy. Besides, its false negative rate was lower than intraoperative biopsy group. So that we advise the surgeons to choose preoperative biopsy when tumor biopsy is considered to be performed in order to improve the accuracy of SLNB.

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Author contribution Zhiyong Yu and Jinming Yu are responsible for the conception of the work. Chenxi Yuan and Xinzhao Wang wrote the manuscript. Zhaoyun Liu and Chao Li made the tables. Mengxue Bian, Jing Shan and Xiang Song was responsible for retrieving the medical record of the enrolled patients. All authors finally approved the manuscript version to be published.

Compliance with ethical standards:

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by Institutional Ethical Committee of Shandong Cancer Hospital and Institute.

Informerd consent Yes.

DISCLOSURE There are no conflicts of interest.

Availability of data and materials

All data analyzed during this study are included in this published article.

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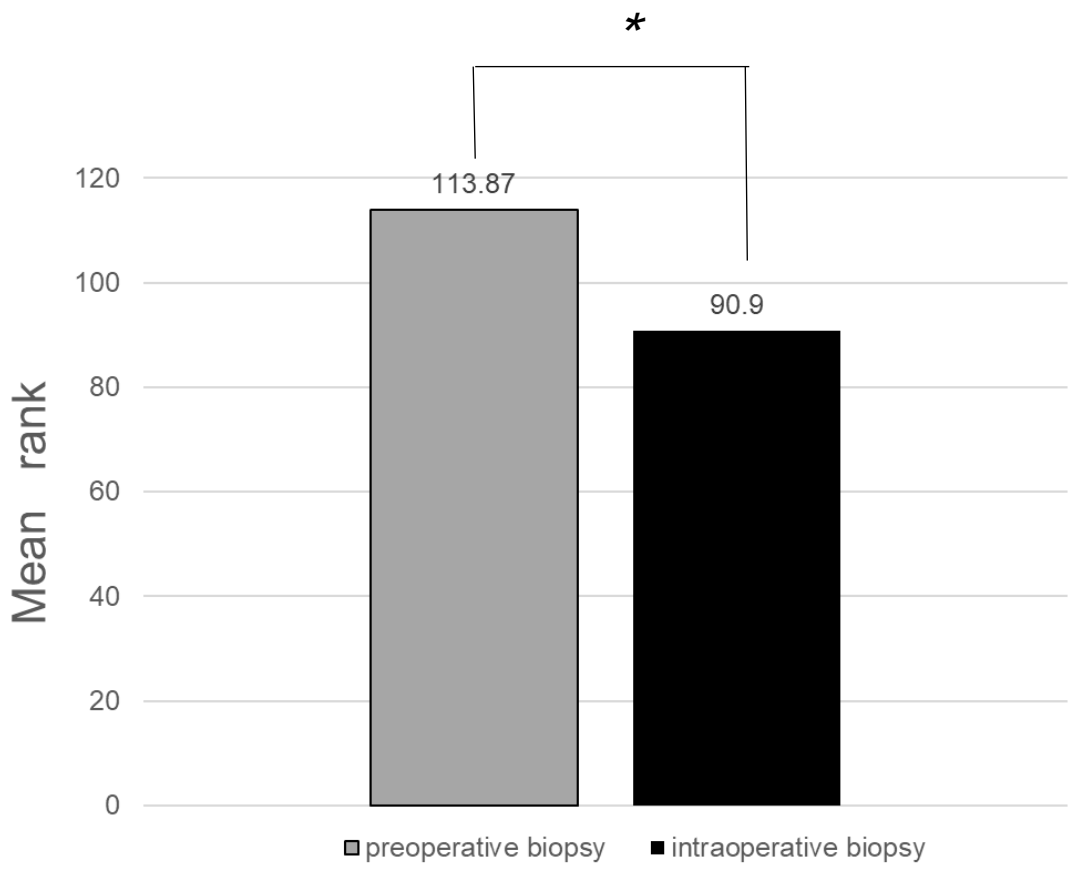
Table 1. Clinicopathologic features

Clinicopathologic characteristic	patients with preoperative biopsy NO. (%)	patients with intraoperative biopsy NO. (%)
Patient age		
≤50 years	52 (48%)	45 (47%)
> 50years	56 (52%)	51 (53%)
Tumor size		
T1	47 (43.5%)	50 (62.5%)
T2	50 (46.3%)	36 (37.5%)
T3	11 (10.2%)	0 (0%)
Tumor location		
Central/subareolar	19 (17.6%)	12 (12.5%)
inner quadrant	30 (27.8%)	27 (28.2%)
outer quadrant	59 (54.6%)	57 (59.3%)

Histologic subtype		
Ductal	105 (97%)	91 (95%)
Lobular	3 (3%)	5 (5%)

Figure 1 . Comparison of identified SLN numbers between preoperative biopsy group and intraoperative biopsy group



* indicate $p < 0.05$

Table 2. Comparison of false negative rate between two groups

	SLN positive	SLN negative	Total	P
Preoperative biopsy	34 (97%)	1 (3%)	35	*0.039**
Intraoperative biopsy	36 (82%)	8 (18%)	44	
Total	70 (89%)	9 (11%)	79	

* indicate $p < 0.05$

Table 3. Subgroup analysis based on tumor location

tumor location		SLNs number 1-2	3-4	⩾5	mean rank	p
Inner quadrant	preoperative biopsy	14	11	5	32.03	0.101
	intraoperative biopsy	17	10	0	25.63	
Outer quadrant	preoperative biopsy	24	30	5	64.61	*0.026**
	intraoperative biopsy	36	17	4	52.18	
subareolar	preoperative biopsy	8	10	1	17.58	0.166
	intraoperative biopsy	8	4	0	13.5	

* indicate $p < 0.05$

Table 4. Subgroup analysis based on tumor stage

tumor stage		SLNs number 1-2	3-4	⩾5	mean rank	p
T1	preoperative biopsy	26	16	5	54.24	0.85
	intraoperative biopsy	32	24	4	52.32	
T2-T3	preoperative biopsy	20	35	6	57.94	*0.002**
	intraoperative biopsy	29	7	0	33.85	

* indicate $p < 0.05$

Table 5. Subgroup analysis based on patient age

Age(years)		SLNs number 1-2	3-4	⩾5	mean rank	p
⩽50	preoperative biopsy	19	29	4	51.25	0.342
	intraoperative biopsy	21	21	3	46.40	
> 50	preoperative biopsy	27	22	7	62.13	***0.003****
	intraoperative biopsy	40	10	1	45.07	

* indicate p < 0.05

Table 6. Subgroup analysis based on duration between preoperative biopsy and surgery

Duration between preoperative biopsy and surgery (days)		SLNs number 1-2	3-4	⩾5	mean rank	p
⩽7	preoperative biopsy	39	45	11	107.64	***0.001****
	intraoperative biopsy	61	31	4	84.48	
⩾8	preoperative biopsy	7	6	0	58.73	0.593
	intraoperative biopsy	61	31	4	54.49	

* indicate p < 0.05